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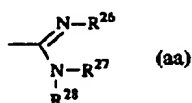
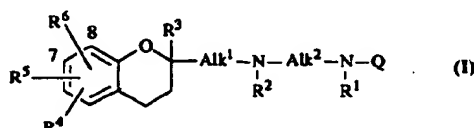
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(54) Title: VASOCONTRICTIVE DIHYDROBENZOPYRAN DERIVATIVES



(57) Abstract

The present invention is concerned with compounds of formula (I), the pharmaceutically acceptable acid addition salts thereof, and the stereochemically isomeric forms thereof, wherein R¹ is hydrogen or C₁-alkyl; R² is hydrogen or C₁-alkyl; R³ is hydrogen or C₁-alkyl; R⁴ is hydrogen, halo, C₁-alkyl, hydroxy, C₁-alkyloxy, aryloxy or arylmethoxy; R⁵ and R⁶ designate R^{5a} and R^{6a}, wherein R^{5a} and R^{6a} taken together form a bivalent radical; or R⁵ and R⁶ can designate R^{5b} and R^{6b}, wherein R^{5b} is hydrogen and R^{6b} is a heterocycle or an optionally substituted alkenyl or alkynyl group; or R⁵ and R⁶ designate R^{5c} and R^{6c}, wherein R^{5c} and R^{6c} are hydrogen, halo, C₁-alkyl, C₃-alkenyl, C₃-alkynyl, hydroxy, C₁-alkyloxy, cyano, aminoC₁-alkyl, carboxyl, C₁-alkyloxycarbonyl, nitro, amino, aminocarbonyl, C₁-alkylcarbonylamino, or mono-di(C₁-alkyl)amino; Q is a heterocyclic ring containing at least one nitrogen atom or a radical of formula (aa), pharmaceutical compositions, preparations and use as a medicine are also described.

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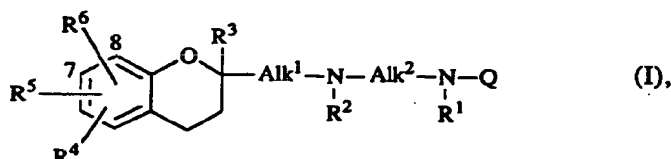
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VASOCONSTRICTIVE DIHYDROBENZOPYRAN DERIVATIVES

5 The present invention relates to novel dihydrobenzopyran derivatives, processes for their preparations, pharmaceutical compositions containing them and their use as a medicine, in particular for the prevention and/or treatment of disorders characterized by excessive vasodilatation, especially migraine.

10 Migraine is a non-lethal disease suffered by one in ten individuals. The main symptom is headache; other symptoms include vomiting and photophobia. For many years the most widely used treatment for migraine involved the administration of ergotalkaloids, which show however several adverse side effects. Recently a tryptamine derivative, i.e. sumatriptan, was introduced as a novel antimigraine drug. We have now surprisingly found that the present novel dihydrobenzopyran derivatives show 5-HT₁-
 15 like agonistic activity and can thus be used in the treatment of disorders characterized by excessive vasodilatation, especially migraine.

The present invention is concerned with compounds of formula



20

the pharmaceutically acceptable acid or base addition salts thereof, and the stereochemically isomeric forms thereof, wherein

R¹, R² and R³ each independently are hydrogen or C₁₋₆alkyl;

R⁴ is hydrogen, halo, C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, aryloxy or arylmethoxy;

25 R⁵ and R⁶ designate R^{5a} and R^{6a},

wherein R^{5a} and R^{6a} are taken together to form a bivalent radical, which is linked to the 7 and 8 position of the dihydrobenzopyran moiety, and has the formula

-CH=CH-CH=CH-	(a1),	-(CH ₂) _t -Z-	(a9),
-(CH ₂) _n -	(a2),	-Z-(CH ₂) _t -	(a10),
-(CH ₂) _m -X-	(a3),	-CH=CH-Z-	(a11),
-X-(CH ₂) _m -	(a4),	-Z-CH=CH-	(a12),
-CH=CH-X-	(a5),	-NH-C(A)=N-	(a13),
-X-CH=CH-	(a6),	-O-C(A)=N-	(a14),
-O-(CH ₂) _t -Y-	(a7),	-N=C(A)-O-	(a15);
-Y-(CH ₂) _t -O-	(a8),		

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in these bivalent radicals one or two hydrogen atoms may be substituted with C_{1-6} alkyl, C_{1-6} alkylcarbonyl or C_{1-6} alkyl-S(O)-;

n is 3 or 4;

each X independently is -O-, -S-, -S(O)-, -S(O)₂-, -C(O)-, -NR⁷-;

5 each m independently is 2 or 3;

each Y independently is -O-, -S-, -S(O)-, -S(O)₂-, -C(O)-, -NR⁷-;

Z is -O-C(O)-, -C(O)-O-, -NH-C(O)-, -C(O)-NH-;

each t independently is 1 or 2;

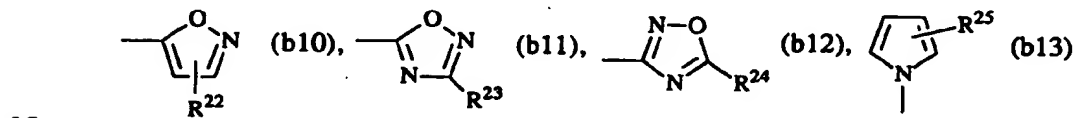
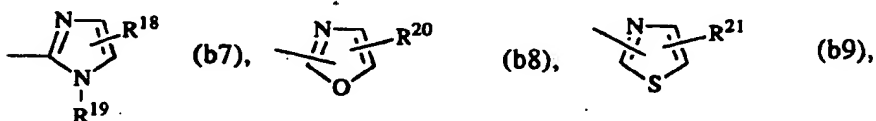
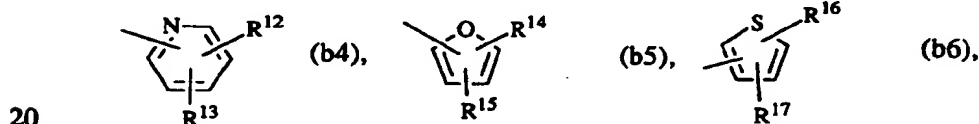
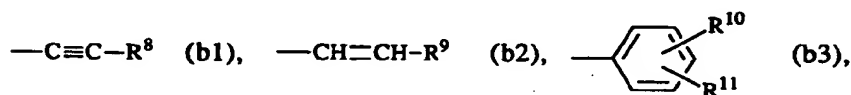
R⁷ is hydrogen, C_{1-6} alkyl, C_{1-6} alkylcarbonyl or C_{1-6} alkyl-S(O)-;

10 each A independently is hydroxy, C_{1-6} alkyl, C_{1-6} alkyloxy;

or R⁵ and R⁶ designate R^{5b} and R^{6b}, wherein R^{5b} is hydrogen and

R^{6b} is hydroxy C_{1-6} alkyl, carboxyl C_{1-6} alkyl, C_{1-6} alkyloxycarbonyl C_{1-6} alkyl, trihalomethyl, C_{1-6} alkylcarbonyl, C_{1-6} alkyloxycarbonyl C_{1-6} alkyl-S-,

15 carboxyl C_{1-6} alkyl-S-, C_{1-6} alkyl-S-, C_{1-6} alkyl-S(O)-, aryl-S-, aryl-S(O)- or R^{6b} is a radical of formula



R⁸ and R⁹ each independently are hydrogen, carboxyl, C_{1-6} alkyloxycarbonyl, aminocarbonyl, mono- or di(C_{1-6} alkyl)aminocarbonyl;

R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶ and R¹⁷ each independently are hydrogen, halo or C_{1-6} alkyl;

30 R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴ and R²⁵ each independently are hydrogen or C_{1-6} alkyl;

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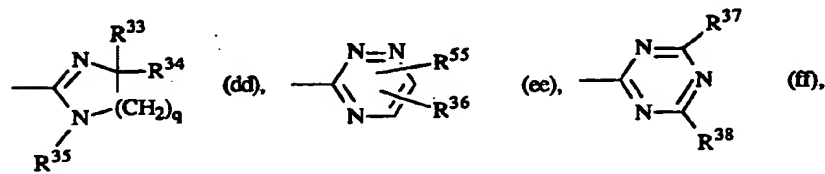
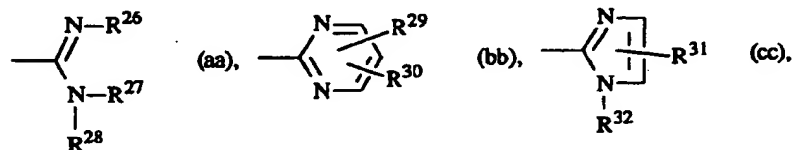
or R^5 and R^6 designate R^{5c} and R^{6c} in which case R^4 can only mean hydrogen;
 and R^{5c} and R^{6c} each independently are hydrogen, halo, C_{1-6} alkyl, C_{3-6} alkenyl,
 C_{3-6} alkynyl, hydroxy, C_{1-6} alkyloxy, cyano, amino C_{1-6} alkyl, carboxyl,
 C_{1-6} alkyloxycarbonyl, nitro, amino, aminocarbonyl, C_{1-6} alkylcarbonylamino, or
 5 mono- or di(C_{1-6} alkyl)amino;

Alk^1 is C_{1-5} alkanediyl;

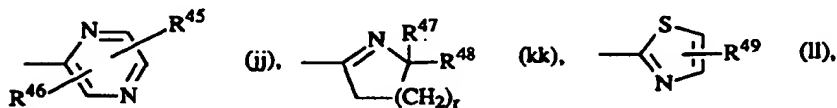
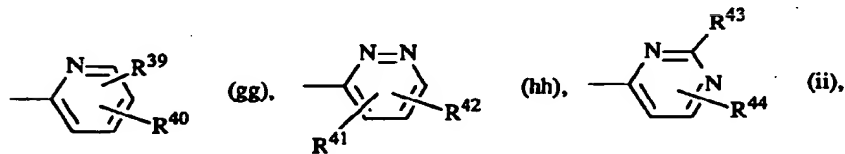
Alk^2 is C_{2-15} alkanediyl;

Q is a radical of formula

10



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20 wherein

R^{26} is hydrogen, cyano, aminocarbonyl or C_{1-6} alkyl;

R^{27} is hydrogen, C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, C_{3-6} cycloalkyl or aryl C_{1-6} alkyl;

R^{28} is hydrogen or C_{1-6} alkyl; or

R^{27} and R^{28} taken together form a bivalent radical of formula $-(CH_2)_4-$, $-(CH_2)_5-$, or a
 25 piperazine which is optionally substituted with C_{1-6} alkyl;

R^{29} , R^{30} , R^{31} , R^{36} , R^{37} , R^{38} , R^{39} , R^{40} , R^{41} , R^{42} , R^{43} , R^{44} , R^{45} , R^{46} , R^{53} , R^{54} and

- R⁵⁵ each independently are hydrogen, hydroxy, halo, C₁₋₆alkyl, C₁₋₆alkyloxy, aryloxy, arylC₁₋₆alkyl, C₁₋₆alkylthio, cyano, amino, mono- or di(C₁₋₆alkyl)amino, mono- or di(C₃₋₆cycloalkyl)amino, aminocarbonyl, C₁₋₆alkyloxycarbonylamino, C₁₋₆alkylaminocarbonylamino, piperidinyl, pyrrolidinyl;
- 5 R³², R³⁵ and R⁵² each independently are hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, or arylC₁₋₆alkyl;
q is 1, 2 or 3;
R³³ and R³⁴ are each hydrogen or taken together with the carbon atom to which they are connected they can form C(O);
- 10 r is 1, 2 or 3;
R⁴⁷ and R⁴⁸ are each hydrogen or taken together with the carbon atom to which they are connected they can form C(O);
R⁴⁹ is hydrogen, halo or C₁₋₆alkyl;
R⁵⁰ is hydrogen and R⁵¹ is hydroxy; or R⁵⁰ and R⁵¹ taken together may form a bivalent
- 15 radical of formula (CH₂)₃ or (CH₂)₄ which is optionally substituted with C₁₋₆alkyl; aryl is phenyl optionally substituted with hydroxy, halo, C₁₋₆alkyl, C₁₋₆alkyloxy;
- with the proviso that when R⁴ is hydrogen and R⁵ and R⁶ designate R^{5c} and R^{6c} then Q must be a radical of formula (gg); (hh); (ii); (jj); (kk); (ll); (mm); (nn); a radical of
- 20 formula (aa) wherein R²⁷ is C₃₋₆cycloalkyl or arylC₁₋₆alkyl; a radical of formula (aa) wherein R²⁷ and R²⁸ taken together with the nitrogen atom to which they are attached form a piperazine which is optionally substituted with C₁₋₆alkyl; a radical of formula (bb) wherein R²⁹ is hydroxy on a carbon atom adjacent to a nitrogen atom; a radical of
- 25 formula (dd) wherein R³⁵ is hydrogen and R³³ and R³⁴ taken together with the carbon atom to which they are attached form C(O); a radical of formula (ee) wherein R⁵⁵ is arylC₁₋₆alkyl.
- Some of the compounds of formula (I) may also exist in their tautomeric forms. Such forms although not explicitly indicated in the above formula are intended to be included
- 30 within the scope of the present invention.
- As used in the foregoing definitions and hereinafter halo defines fluoro, chloro, bromo and iodo; C₁₋₆alkyl defines straight and branch chained saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as, for example, methyl, ethyl, propyl, butyl,
- 35 pentyl, hexyl and the like; C₃₋₆alkenyl defines straight and branch chained hydrocarbon radicals containing one double bond and having from 3 to 6 carbon atoms, such as, for example, 2-propenyl, 3-butenyl, 2-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl and the like; and the carbon atom of said C₃₋₆alkenyl being connected to a nitrogen atom

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preferably is saturated, C₃₋₆alkynyl defines straight and branch chained hydrocarbon radicals containing one triple bond and having from 3 to 6 carbon atoms, such as, for example, 2-propynyl, 3-butylnyl, 2-butylnyl, 2-pentylnyl, 3-pentylnyl, 3-hexynyl, and the like; and the carbon atom of said C₃₋₆alkynylradical being connected to a nitrogen atom

5 preferably is saturated; C₃₋₆cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; C₁₋₅alkanediyl defines bivalent straight and branch chained saturated hydrocarbon radicals having from 1 to 5 carbon atoms, such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl or 1,5-pentanediyl and the branched isomers thereof; C₂₋₁₅alkanediyl defines bivalent straight and branch chained saturated

10 hydrocarbon radicals having from 2 to 15 carbon atoms such as, for example, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,5-pentanediyl, 1,6-hexanediyl, 1,7-heptanediyl, 1,8-octanediyl, 1,9-nonanediyl, 1,10-decanediyl, 1,11-undecanediyl, 1,12-dodecanediyl, 1,13-tridecanediyl, 1,14-tetradecanediyl, 1,15-pentadecanediyl, and the branched isomers thereof. The terms C₁₋₄alkanediyl, C₂₋₆alkanediyl and

15 C₂₋₁₄alkanediyl are defined in an analogous manner. The term "C(O)" refers to a carbonyl group.

The pharmaceutically acceptable acid addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the

20 compounds of formula (I) are able to form. The latter can conveniently be obtained by treating the base form with such appropriate acids as inorganic acids, for example, hydrohalic acids, e.g. hydrochloric, hydrobromic and the like; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic,

25 (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzene-sulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted by treatment with alkali into the free base form.

30 The compounds of formula (I) containing acidic protons may also be converted into their therapeutically active non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g.

35 the benzathine, N-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like. Conversely the salt form can be converted by treatment with acid into the free acid form.

The term addition salt also comprises the hydrates and solvent addition forms which the compounds of formula (I) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

- 5 The term "stereochemically isomeric forms" as used hereinbefore defines all the possible isomeric forms which the compounds of formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. More in particular,
- 10 stereogenic centers may have the R- or S-configuration; substituents on bivalent cyclic saturated hydrocarbon radicals may have either the cis- or trans-configuration and C₃₋₆-alkenyl radicals may have the E- or Z-configuration. Stereochemically isomeric forms of the compounds of formula (I) are obviously intended to be embraced within the scope of this invention.
- 15 R¹ is suitably methyl or hydrogen, preferably R¹ is hydrogen;
R² is suitably methyl or hydrogen, preferably R² is hydrogen;
R³ is suitably methyl or hydrogen, preferably R³ is hydrogen;
R⁴ is suitably hydrogen, C₁₋₆-alkyl or C₁₋₆-alkyloxy, preferably R⁴ is hydrogen;
20 when R⁵ and R⁶ designate R^{5a} and R^{6a},
 then R^{5a} and R^{6a} suitably form a bivalent radical of formula (a1), (a2), (a3), (a4), (a7), (a8), (a11) or (a12);
 X is suitably O, S or S(O)₂, preferably X is O or S(O)₂;
 Y is suitably O or S, preferably Y is O;
25 Z is suitably -O-C(O)- or -C(O)-O-;
 when R⁵ and R⁶ designate R^{5b} and R^{6b},
 then R^{6b} suitably is hydroxyC₁₋₆-alkyl, trihalomethyl, or a radical of formula (b1), (b2), (b3), (b4), (b5), (b6) or (b13);
 R^{6b} preferably is in the 8-position of the dihydrobenzopyran moiety;
30 R⁸ is suitably hydrogen or C₁₋₆-alkyloxycarbonyl, preferably R⁶ is hydrogen;
R⁹ is suitably hydrogen or C₁₋₆-alkyloxycarbonyl, preferably R⁷ is hydrogen or methyloxycarbonyl;
R¹⁰ and R¹¹ each independently are suitably hydrogen or C₁₋₆-alkyl, preferably R¹⁰ and R¹¹ are hydrogen or methyl;
35 R¹² and R¹³ each independently are suitably hydrogen or hydroxy;
R¹⁴ and R¹⁵ each independently are suitably hydrogen or C₁₋₆-alkyl, preferably R¹⁴ and R¹⁵ are hydrogen;
R¹⁶ and R¹⁷ each independently are hydrogen or C₁₋₆-alkyl, preferably R¹⁶ and R¹⁷

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- are both hydrogen;
R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴ and R²⁵ are preferably hydrogen;
when R⁵ and R⁶ designate R^{5c} and R^{6c};
then R^{5c} and R^{6c} suitably are hydrogen, halo, or C₁₋₆alkyl, preferably R^{5c} and R^{6c} are
5 hydrogen, chloro, fluoro, methyl or ethyl;
Alk¹ is suitably C₁₋₃alkanediyl, preferably Alk¹ is methylene;
Alk² is suitably C₂₋₆alkanediyl, preferably Alk² is 1,3-propanediyl;
when Q is a radical of formula (aa),
R²⁶ is suitably hydrogen, cyano, aminocarbonyl or methyl, preferably R²⁶ is hydrogen
10 or cyano;
R²⁷ is suitably hydrogen or C₁₋₆alkyl, preferably R²⁷ is hydrogen, methyl or ethyl;
R²⁸ is suitably hydrogen or C₁₋₆alkyl, preferably R²⁸ is hydrogen or methyl;
a radical of formula (bb),
R²⁹ and R³⁰ each independently are suitably hydrogen, hydroxy, halo, methyl,
15 preferably both R²⁹ and R³⁰ are hydrogen or R²⁹ is hydrogen and R³⁰ is hydroxy;
a radical of formula (cc),
R³¹ is suitably hydrogen, hydroxy, preferably R³¹ is hydrogen;
R³² is suitably hydrogen, or phenylmethyl, preferably R³² is hydrogen;
a radical of formula (dd),
20 q is preferably 2;
R³³ and R³⁴ are both preferably hydrogen;
R³⁵ is suitably hydrogen or phenylmethyl, preferably R³⁵ is hydrogen;
a radical of formula (ee),
R³⁶ is suitably hydrogen, halo or methyl, preferably R³⁶ is hydrogen or chloro;
25 R³⁵ is suitably hydrogen or phenylmethyl;
a radical of formula (ff),
R³⁷ and R³⁸ each independently suitably are hydrogen, halo or methyl, preferably R³⁷
and R³⁸ are hydrogen or chloro;
a radical of formula (gg),
30 R³⁹ and R⁴⁰ each independently suitably are hydrogen, hydroxy, chloro or methyl,
preferably R³⁹ and R⁴⁰ are both hydrogen or R³⁹ is hydrogen and R⁴⁰ is hydroxy;
a radical of formula (hh),
R⁴¹ and R⁴² each independently suitably are hydrogen, hydroxy, halo or methyl,
preferably R⁴¹ and R⁴² are both hydrogen or R⁴¹ is hydrogen and R⁴² is chloro;
35 a radical of formula (ii),
R⁴³ and R⁴⁴ each independently suitably are hydrogen, halo, C₁₋₆alkyloxy,
C₁₋₆alkylthio, amino, mono- or di(C₁₋₆alkyl)amino, preferably R⁴³ is hydrogen,

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- chloro, methylthio or amino and R^{44} is hydrogen;
 a radical of formula (jj),
 R^{45} and R^{46} each independently suitably are hydrogen, halo, C_1 -alkyl, preferably
 R^{45} and R^{46} are hydrogen or chloro;
 5 a radical of formula (kk),
 r preferably is 2;
 R^{47} and R^{48} both preferably are hydrogen;
 a radical of formula (ll),
 R^{49} is suitably hydrogen or methyl, preferably hydrogen;
 10 a radical of formula (mm),
 R^{50} and R^{51} taken together suitably form a bivalent radical of formula $(CH_2)_4$;
 R^{52} suitably is hydrogen;
 a radical of formula (nn),
 R^{53} is suitably hydrogen and R^{54} suitably is hydroxy; and
 15 aryl is preferably phenyl.

A group of special compounds are those compounds of formula (I) wherein R^1 , R^2 , R^3 and R^4 are as defined under formula (I) and wherein R^5 and R^6 designate R^{5a} and R^{6a} , wherein in formulas (a7) and (a8) t is 2; Q is a radical of formula (aa), (bb), (cc),
 20 (dd) wherein q is 1 or 2, (ee) wherein R^{55} is hydrogen, (ff), (gg), (hh), (ii), (jj), (kk) wherein q is 1 or 2, (ll).

Another group of special compounds are those compounds of formula (I) wherein R^1 , R^2 , R^3 are as defined under formula (I), R^4 is hydrogen, halo, C_1 -alkyl; R^5 and R^6
 25 designate R^{5b} and R^{6b} , R^{5b} being hydrogen and R^{6b} is hydroxy C_1 -alkyl, carboxyl C_1 -alkyl, C_1 -alkyloxycarbonyl C_1 -alkyl, trihalomethyl, a radical of formula (b1), (b2), (b3), (b4), (b5), (b6), (b7), (b8), (b9), (b10), (b11), (b12); Q is a radical of formula (aa), (bb), (cc), (dd) wherein q is 1 or 2, (ee) wherein R^{55} is hydrogen, (ff), (gg), (hh), (ii), (jj), (kk) wherein q is 1 or 2, or (ll).
 30

Still another group of special compounds are those compounds of formula (I) wherein R^1 , R^2 , R^3 are as defined under formula (I), R^4 is hydrogen and R^5 and R^6 designate R^{5c} and R^{6c} , and Q is a radical of formula (gg); (hh); (ii); (jj); (kk) wherein q is 1 or 2;
 (ll); a radical of formula (bb) wherein R^{29} is hydroxy on a carbon atom adjacent to a
 35 nitrogen atom; or a radical of formula (dd) wherein R^{35} is hydrogen and R^{33} and R^{34} taken together with the carbon atom to which they are attached form $C(O)$ and q is 1 or 2.

Interesting compounds are those compounds of formula (I), wherein R² is hydrogen.

Also interesting compounds are those compounds of formula (I) wherein R³ is hydrogen.

5

Particular compounds are those compounds of formula (I) wherein R⁵ and R⁶ designate R^{5a} and R^{6a} and Q is a radical of formula (bb) wherein R²⁹ and R³⁰ are hydrogen; or Q is a radical of formula (dd) wherein q is 1 or 2 and R³¹ and R³² are both hydrogen.

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Also particular compounds are those compounds of formula (I) wherein R⁵ and R⁶ designate R^{5b} and R^{6b}, R^{5b} being hydrogen and R^{6b} is C₁-alkyloxycarbonyl-C₁-alkyl, trihalomethyl, C₁-alkyloxycarbonyl-C₁-alkyl-S-, C₁-alkyl-S-, aryl-S-, aryl-S(O)-, or R^{6b} is a radical of formula (b1), wherein R⁸ is hydrogen; (b2) wherein R⁹ is C₁-alkyloxycarbonyl; (b3) wherein R¹⁰ and R¹¹ both being hydrogen; (b4) wherein R¹² and R¹³ are both hydrogen; (b5) wherein R¹⁴ and R¹⁵ are both hydrogen; (b6) R¹⁶ is hydrogen or halo and R¹⁷ is hydrogen; or (b13) wherein R²⁵ is hydrogen; Q is a radical of formula (bb) wherein R²⁹ and R³⁰ are hydrogen; or Q is a radical of formula (dd) wherein q is 1 or 2 and R³¹ and R³² are both hydrogen.

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Still other particular compounds are those compounds of formula (I) wherein R⁴ is hydrogen; R⁵ and R⁶ designate R^{5c} and R^{6c}, R^{5c} being hydrogen and R^{6c} is hydrogen, halo, C₁-alkyl or C₁-alkyloxy; Q is a radical of formula (aa) wherein R²⁶ is hydrogen, cyano or aminocarbonyl, R²⁷ is arylC₁-alkyl and R²⁸ is hydrogen or C₁-alkyl, or R²⁷ and R²⁸ taken together with the nitrogen atom to which they are attached form are piperazine ring which is N-substituted with C₁-alkyl; a radical of formula (bb) wherein R²⁹ is hydroxy on a carbon atom adjacent to a nitrogen atom; a radical of formula (dd) wherein R³⁵ is hydrogen and R³³ and R³⁴ taken together with the carbon atom to which they are attached form C(O); a radical of formula (ee) wherein R³⁶ is hydroxy and R⁵⁵ is arylC₁-alkyl; a radical of formula (gg) wherein R³⁹ and R⁴⁰ each independently are hydrogen, C₁-alkyl or aminocarbonyl; a radical of formula (hh) wherein R⁴¹ and R⁴² each independently are hydrogen, halo, hydroxy, C₁-alkyl or aminocarbonyl; a radical of formula (ii) wherein R⁴⁴ is hydrogen and R⁴³ is hydrogen, C₁-alkyloxy, C₁-alkylthio, amino, mono- or di(C₁-alkyl)amino, piperidinyl; a radical of formula (jj) wherein R⁴⁵ and R⁴⁶ are both hydrogen; a radical of formula (kk) wherein R⁴⁷ and R⁴⁸ are both hydrogen; a radical of formula (ll) wherein R⁴⁹ is hydrogen; a radical of formula (mm) wherein R⁵⁰ is hydrogen, R⁵¹ is hydroxy or R⁵⁰ and R⁵¹ taken together form a bivalent radical of formula (CH₂)₄ and R⁵² is hydrogen; or a radical of formula (nn) wherein R⁵³ is hydrogen and R⁵⁴

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is hydroxy.

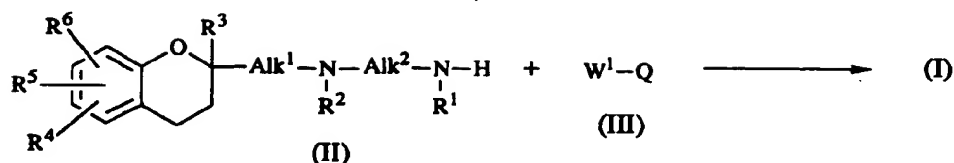
Preferred compounds are :

- \underline{N} -[(2,3,4,7,8,9-hexahydrobenzo[2,1-b:3,4-b']dipyran-2-yl)methyl]- \underline{N}' -
 5 2-pyrimidinyl-1,3-propanediamine; \underline{N} -[(2,3,4,7,8,9-hexahydrocyclopenta[h]-
 1-benzopyran-2-yl)methyl]- \underline{N}' -2-pyrimidinyl-1,3-propanediamine; (\pm)- \underline{N} -[(2,3,4,8,9,
 10-hexahydrobenzo[2,1-b:3,4-b']dipyran-2-yl)methyl]- \underline{N}' -2-pyrimidinyl-1,3-propane
 diamine; \underline{N} -[(3,4,7,8,9,10-hexahydro-2H-naphtho[1,2-b]pyran-2-yl)methyl]-
 \underline{N}' -2-pyrimidinyl-1,3-propanediamine; \underline{N} -(4,5-dihydro-1H-imidazol-2-yl)- \underline{N}' -
 10 [(2,3,4,7,8,9-hexahydrocyclopenta[h]-1-benzopyran-2-yl)methyl]-1,3-propanediamine;
 \underline{N} -[(2,3,4,7,8,9-hexahydrobenzo[2,1-b:3,4-b']dipyran-2-yl)methyl]- \underline{N}' -(1,4,5,6-
 tetrahydro-2-pyrimidinyl)-1,3-propanediamine; \underline{N} -[(2,3,4,7,8,9-hexahydro
 cyclopenta[h]-1-benzopyran-2-yl)methyl]- \underline{N}' -(1,4,5,6-tetrahydro-2-pyrimidinyl)-
 1,3-propanediamine; \underline{N} -[(2,3,7,8-tetrahydro-9H-pyrano[2,3-f]-1,4-benzodioxin-9-
 15 yl)methyl]- \underline{N}' -(1,4,5,6-tetrahydro-2-pyrimidinyl)-1,3-propanediamine;
 \underline{N} -[(3,4,7,8,9,10-hexahydro-2H-naphtho[1,2-b]pyran-2-yl)methyl]- \underline{N}' -(1,4,5,6-
 tetrahydro-2-pyrimidinyl)-1,3-propanediamine;
 methyl 3-[6-fluoro-3,4-dihydro-2-[[[3-(2-pyrimidinylamino)propyl]amino]methyl]-2H-
 1-benzopyran-8-yl]-2-propenoate; \underline{N} -[[6-fluoro-8-(2-furanyl)-3,4-dihydro-
 20 2H-1-benzopyran-2-yl)methyl]- \underline{N}' -2-pyrimidinyl-1,3-propanediamine;
 \underline{N} -[[6-fluoro-3,4-dihydro-8-(2-thienyl)-2H-1-benzopyran-2-yl)methyl]- \underline{N}' -(1,4,5,6-
 tetrahydro-2-pyrimidinyl)-1,3-propanediamine;
 \underline{N} -[(3,4-dihydro-2H-1-benzopyran-2-yl)methyl]- \underline{N}' -(3,4,5,6-tetrahydro-
 2-pyridinyl)-1,3-propanediamine; \underline{N}^4 -[3-[[[(3,4-dihydro-2H-1-benzopyran-
 25 2-yl)methyl]amino]propyl]- \underline{N}^2 -methyl-2,4-pyrimidinediamine, the pharmaceutically
 acceptable acid addition salts thereof and the stereochemically isomeric forms thereof.

The compounds of formula (I) can generally be prepared by reacting a diamine of
 formula (II) with a reagent of formula (III) wherein W^1 is a reactive leaving group such
 30 as, for example, halo, e.g. chloro, bromo; alkyloxy, e.g. methoxy, ethoxy and the like;
 aryloxy, e.g. phenoxy and the like; alkylthio, e.g. methylthio, ethylthio and the like;
 arylthio, e.g. benzenethio and the like.

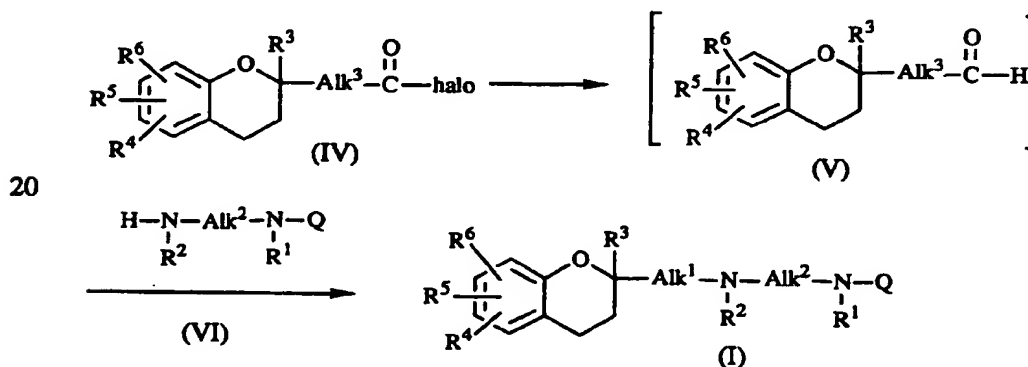
In the formulas (II), (III) and all the following formulas the variabls R^1 , R^2 , R^3 , R^4 ,
 R^5 , R^6 , Alk^1 , Alk^2 , and Q are as defined under formula (I) unless specifically described
 35 otherwise.

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Said reaction can be performed by stirring the diamine of formula (II) with the reagent of formula (III) in an appropriate solvent such as, for example, an alcohol, e.g. ethanol and the like; a halogenated hydrocarbon, e.g. trichloromethane and the like or an ether, e.g. tetrahydrofuran, 1,4-dioxane and the like; an aromatic hydrocarbon, e.g. methylbenzene and the like or mixtures thereof. Optionally a base, such as, for example, an alkalimetal carbonate, e.g. sodium or potassium carbonate; an alkalimetal hydrogen carbonate, e.g. sodium or potassium hydrogen carbonate; an appropriate organic base, e.g. *N,N*-diethylethanamine, pyridine and the like bases, can be added to pick up the acid that may be formed during the course of the reaction. Elevated temperatures may enhance the rate of the reaction. Preferably the reaction is performed at the reflux temperature of the reaction mixture.

The compounds of formula (I) can also generally be prepared by reductive *N*-alkylation of an aminoderivative of formula (VI) with an appropriate aldehyde of formula (V), wherein Alk^3 is a direct bond or C_{1-4} alkanediyl.



Said reaction is performed by stirring the reactants in an appropriate solvent such as, for example, an alcohol, e.g. ethanol and the like; an ether, e.g. tetrahydrofuran and the like; an aromatic solvent, e.g. methylbenzene and the like, or mixtures thereof. Optionally a water separator can be used to remove the water that is formed during the course of the reaction. The resulting imine can then be reduced by reactive hydride reagents such as, for example, sodium borohydride, or by catalytic hydrogenation on an appropriate catalyst, such as, for example palladium on charcoal, platinum on charcoal, Raney nickel

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and the like in a suitable solvent, such as, for example an alcohol, e.g. methanol, ethanol and the like; an ether, e.g. tetrahydrofuran, and the like; a carboxylic ester, e.g. ethyl acetate, butyl acetate and the like; or a carboxylic acid, e.g. acetic acid, propanoic acid and the like. Optionally the reaction may be performed at elevated temperatures and/or pressures.

The intermediate aldehyde of formula (V) can be prepared by reducing an acyl derivative of formula (IV) wherein Alk^3 is defined as above. The acyl halide can be prepared by reacting the corresponding acid, with a halogenating reagent such as thionylchloride, phosphorus trichloride, phosphorus tribromide, oxalylchloride and the like. The latter reaction may be performed in an excess of the halogenating reagent or in appropriate solvents such as for example halogenated hydrocarbons, e.g. dichloromethane, trichloromethane and the like; aromatic hydrocarbons, e.g. methylbenzene and the like; ethers, e.g. tetrahydrofuran, 1,4-dioxane and the like, or dipolar aprotic solvents, e.g. N,N-dimethylformamide, N,N-dimethylacetamide and the like. Stirring and elevated temperatures may be appropriate to enhance the rate of the reaction.

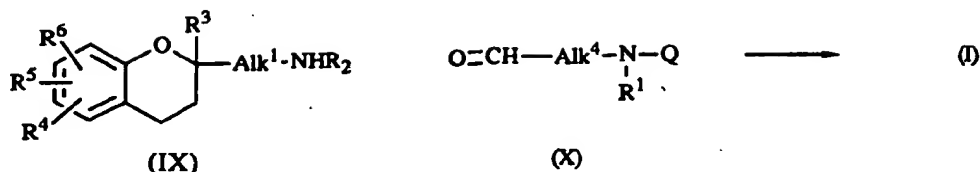
Said reduction of the acylhalide of formula (IV) can for instance be performed by catalytic hydrogenation with a catalyst such as palladium on charcoal, palladium on bariumsulfate, platinum on charcoal and the like in appropriate solvents such as, for example ethers, e.g. tetrahydrofuran and the like; preferably in admixture with a dipolar aprotic solvent, such as, for example N,N-dimethylformamide, N,N-dimethylacetamide and the like. Optionally a catalyst poison can be added, such as thiophene, quinoline-sulfur and the like.

The reaction sequence starting from the intermediate of formula (IV) and yielding compounds of formula (I) may be performed as a one-pot procedure.

The intermediates of formula (V) wherein R^5 and R^6 designate R^{5a} and R^{6a} are defined as intermediates of formula (V-a); intermediates of formula (V) wherein R^5 and R^6 designate R^{5b} and R^{6b} are defined as intermediates of formula (V-b). The intermediates of formula (V-a) and (V-b) are deemed novel.

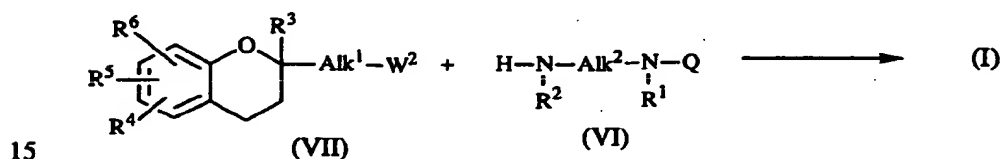
The compounds of formula (I) can also be prepared by reductive N-alkylation of an amine of formula (IX) with an aldehyde of formula (X), wherein Alk^4 is C_{2-14} alkanediyl. The reaction conditions are similar to those described for the reaction of intermediates of formula (V) with those of formula (VI).

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The intermediates of formula (IX) wherein R⁵ and R⁶ designate R^{5a} and R^{6a} are indicated hereinunder as intermediates of formula (IX-a); intermediates of formula (IX) wherein R⁵ and R⁶ designate R^{5b} and R^{6b} are indicated hereinunder as intermediates of
 5 formal (IX-b). The intermediates of formula (IX-a) and (IX-b) are deemed novel.

The compounds of formula (I) can also be prepared by N-alkylating an amine of formula (VI) with an intermediate of formula (VII), wherein W² is a reactive leaving group such as, for example, halo, e.g. chloro, bromo or iodo; sulfonyloxy, e.g.
 10 methanesulfonyloxy, methylbenzenesulfonyloxy and the like, in appropriate solvents such as ketones, e.g. 2-butanone and the like; ethers, e.g. tetrahydrofuran and the like; aromatic hydrocarbons, e.g. methylbenzene and the like; dipolar aprotic solvents, e.g. N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide and the like.



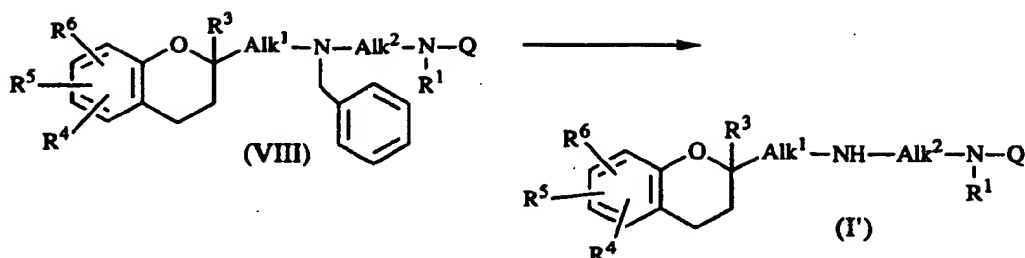
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Stirring and heating may enhance the reaction rate. Optionally a suitable base may be added to pick up the acid that is formed during the course of the reaction, such as, for example an alkali metal carbonate, e.g. sodium or potassium carbonate; an alkali metal
 20 hydrogen carbonate, e.g. sodium or potassium hydrogen carbonate and the like; an appropriate organic base, e.g. N,N-diethylethanamine, pyridine and the like.

The intermediates of formula (VII) wherein R⁵ and R⁶ designate R^{5a} and R^{6a} are indicated hereinunder as intermediates of formula (VII-a); intermediates of formula (VII) wherein R⁵ and R⁶ designate R^{5b} and R^{6b} are indicated hereinunder as intermediates of
 25 formal (VII-b). The intermediates of formula (VII-a) and (VII-b) are deemed novel.

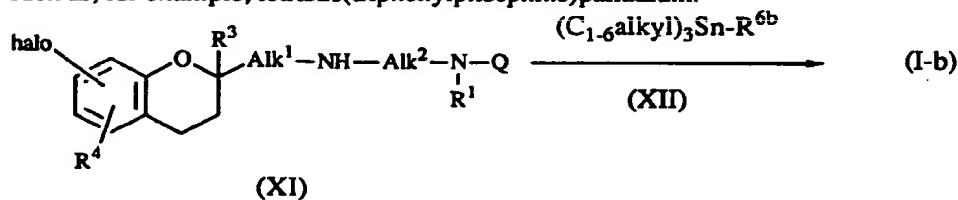
The compounds of formula (I), wherein R² is hydrogen, said compounds being
 30 represented by formula (I'), may be prepared by debenzylation of an intermediate of formula (VIII).

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Said debenzylation can be performed following art-known procedures such as catalytic hydrogenation using appropriate catalysts, e.g. platinum on charcoal, palladium on charcoal, in appropriate solvents such as alcohols, e.g. methanol, ethanol, 2-propanol and the like; ethers e.g. 1,1'-oxybisethane, tetrahydrofuran, 2,2'-oxybispropane and the like. Optionally elevated temperatures and pressures may be applied.

Compounds of formula (I) wherein R^5 and R^6 designate R^{5b} and R^{6b} are indicated as compounds of formula (I-b). Compounds of formula (I-b) may be prepared by aromatic substitution of a halosubstituted, preferably iodosubstituted, dihydrobenzopyran derivative of formula (XI). Said aromatic substitution may, for instance, be carried out with a reagent of formula (XII) in suitable solvent and in the presence of an appropriate catalyst, such as, for example, tetrakis(triphenylphosphine)palladium.



The compounds of formula (I), can also be converted into each other by functional group transformations. For instance the compounds of formula (I), wherein Q represents a pyrimidinyl or a pyridinyl moiety can be converted into the tetrahydroanalogs following art-known catalytic hydrogenation procedures. Furthermore, compounds of formula (I) bearing a C_{3-6} alkynylgroup or C_{3-6} alkenylgroup can be converted into the corresponding compounds bearing C_{1-6} alkylgroup following art-known hydrogenation techniques. Compounds of formula (I) bearing a cyanogroup can be converted into the corresponding compounds bearing an aminomethyl substituent following art-known hydrogenation techniques. Compounds bearing an alkyloxy substituent can be converted into compounds bearing a hydroxy group by treating the alkyloxy compound with an appropriate acidic reagent such as for example, hydrohalic acid, e.g. hydrobromic acid or borontribromide and the like. Compounds bearing an amino substituent can be N-acylated or N-alkylated following art-known N-acylation or N-alkylation procedures.

The intermediates mentioned hereinabove are novel and may be prepared following art-known procedures which are for instance illustrated in the experimental part.

- 5 Pure stereochemically isomeric forms of the compounds of this invention may be obtained by the application of art-known procedures. Diastereoisomers may be separated by physical separation methods such as selective crystallization and chromatographic techniques, e.g. liquid chromatography. Enantiomers may be separated from each other by the selective crystallization of their diastereomeric salts with optically active acids.
- 10 Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.
- 15 The compounds of formula (I), the pharmaceutically acceptable acid-addition salts and stereochemically isomeric forms thereof have interesting pharmacological properties : they show 5HT₁-like agonistic activity. The compounds of the present invention have remarkable vasoconstrictor activity. They are useful to prevent or treat conditions which are related to vasodilatation. For instance, they are useful in the treatment of conditions
- 20 characterized by or associated with cephalic pain, e.g. cluster headache and headache associated with vascular disorders, especially migraine. These compounds are also useful in the treatment of venous insufficiency and in the treatment of conditions associated with hypotension.
- 25 The vasoconstrictor activity of the compounds of formula (I) can be determined using an in vitro-test as is described in "Instantaneous changes of alpha-adrenoreceptor affinity caused by moderate cooling in canine cutaneous veins" in the American Journal of Physiology 234(4), H330-H337, 1978; or in the test described in the pharmacological example, wherein the serotonin-like response of the compounds of the present invention
- 30 was tested on the basilar arteries of pigs.

- In view of their useful pharmacological properties, the subject compounds may be formulated into various pharmaceutical forms for administration purposes.
- To prepare the pharmaceutical compositions of this invention, an effective amount of a
- 35 particular compound, in base or acid addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form

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suitable, preferably, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, to aid solubility for example, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause a significant deleterious effect to the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment. It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

The compounds of the present invention therefore may be used as medicines in conditions related to vasodilatation, more in particular hypotension, venous insufficiency and especially cephalic pain among which migraine. The compounds of the present invention also provide a method of treating warm-blooded animals suffering from conditions related to vasodilatation, such as, hypotension, venous insufficiency and especially cephalic pain among which migraine by administering an effective amount of a compound of formula (I), a pharmaceutically acceptable acid addition salt or a stereoisomeric form thereof. Those skilled in the art could easily determine the effective

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amount from the test results presented hereinafter. In general it is contemplated that an effective amount would be from 1 µg/kg to 1 mg/kg body weight, and in particular from 2 µg/kg to 200 µg/kg body weight. It may be appropriate to administer the required dose as two, three, four or more sub-doses at appropriate intervals throughout the day. Said
5 sub-doses may be formulated as unit dosage forms, for example, containing 0.005 to 20 mg, and in particular 0.1 mg to 10 mg of active ingredient per unit dosage form.

The following examples are intended to illustrate and not to limit the scope of the present invention in all its aspects.

10

Experimental part

A. Preparation of compounds of formula (I) wherein R⁵ and R⁶ designate R^{5a} and R^{6a}, and the intermediates thereof.

15 Example 1-a

a) A mixture of 2,3-dihydro-1H-inden-4-ol (0.37mol) and acetic anhydride (0.37mol) in sulfuric acid (300ml) was stirred for 1 hour at room temperature. The reaction mixture was poured out into a mixture of water and 1,1'-oxybisethane. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated, yielding 75g (>100%
20 crude residue) of 2,3-dihydro-1H-inden-4-ol acetate (ester) (interm. 1-a).

b) Intermediate (1-a) (0.37mol) was heated to 100°C. Aluminum chloride (200g) was added and the reaction mixture was stirred for 1 hour at 120°C. The reaction mixture was cooled and ice was added, followed by a mixture of water and concentrated hydrochloric acid. This mixture was extracted with 1,1'-oxybisethane. The organic layer was
25 separated, treated with activated charcoal, dried (MgSO₄), filtered and the filtrate was evaporated. The residue was purified by distillation (oil pump; 110°C), yielding 29g of 1-(2,3-dihydro-4-hydroxy-1H-inden-5-yl)ethanone (interm. 2-a).

c) Sodium methylate (24g) was stirred in methylbenzene (300ml). A mixture of diethyl oxalate (0.16mol) and intermediate (2-a) (0.16mol) in methylbenzene (10ml) was added dropwise. This mixture was stirred and refluxed for 2 hours. The resulting precipitate
30 was filtered off and dried. The solid was stirred in a mixture of hydrochloric acid (10ml) and acetic acid (500ml). The reaction mixture was stirred and refluxed for 1 hour. The mixture was poured out into water. The resulting precipitate was filtered off and dried (vacuum), yielding 21g of 4,7,8,9-tetrahydro-4-oxocyclopenta[h]-1-benzopyran-
35 2-carboxylic acid (interm. 3-a).

d) A mixture of intermediate (3-a) (0.09mol) in acetic acid (200ml) was hydrogenated with palladium on activated carbon (1g) as a catalyst. After uptake of hydrogen (3 eq.), the catalyst was filtered off. The solvent was evaporated. The residue was vacuum

dried, yielding 21g of (±)-2,3,4,7,8,9-hexahydrocyclopenta[h]-1-benzopyran-2-carboxylic acid (interm. 4-a).

- 5 e) A mixture of intermediate (4-a) (0.11 mol) in tetrahydrofuran (250ml) was stirred under nitrogen flow. 1,1'-Carbonylbis-1H-imidazole (0.11 mol) was added and the reaction mixture was stirred for 2 hours at room temperature. Then, it was cooled to -80°C. A solution of diisobutylaluminum hydride in methylbenzene (20%) (0.33 mol) was added dropwise and the reaction mixture was stirred for 2 hours at -80°C. The mixture was decomposed with methanol, then poured out into water. The mixture was acidified, then extracted with 1,1'-oxybisethane. The separated organic layer was dried (MgSO₄), filtered and the solvent was evaporated, yielding 12g of (±)-2,3,4,7,8,9-hexahydrocyclopenta[h]-1-benzopyran-2-carboxaldehyde (interm. 5-a).
- 10 In a similar manner were also prepared :
- (±)-2,3,7,8-tetrahydro-9H-pyrano[2,3-f]-1,4-benzodioxin-9-carboxaldehyde (interm. 6-a);
- 15 (±)-2,3,4,8,9,10-hexahydrobenzo[1,2-b:3,4-b']dipyrans-2-carboxaldehyde (interm. 7-a);
- (±)-2,3,4,7,8,9-hexahydrobenzo[2,1-b:3,4-b']dipyrans-2-carboxaldehyde (interm. 8-a).

Example 2-a

- 20 a) A mixture of 4-oxo-4H-naphtho[1,2-b]pyran-2-carboxylic acid (12g) and 2-methoxyethanol (100ml) was hydrogenated at normal pressure and at room temperature in the presence of palladium on activated carbon 10% (2g) as a catalyst. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated, yielding 7g (61.4%) of 3,4-dihydro-2H-naphtho[1,2-b]pyran-2-carboxylic acid (interm. 9-a).
- 25 b) A mixture of intermediate (9-a) (7g), ethanol (160ml) and sulfuric acid was stirred and refluxed for 1 hour. The reaction mixture was evaporated and the oily residue was taken up in water. After treating with sodium hydroxide, the product was extracted with dichloromethane. The extract was dried, filtered and evaporated, yielding 5g (63.5%) of ethyl 3,4-dihydro-2H-naphtho[1,2-b]pyran-2-carboxylate (interm. 10-a).
- 30 c) A mixture of intermediate (10-a) (0.03 mol) in methanol saturated with ammonia (200ml) was stirred at room temperature overnight. The precipitate was filtered off and washed with methanol. The product was used without further purification, yielding 6.6g (97%) of (±)-3,4-dihydro-2H-naphtho[1,2-b]pyran-2-carboxamide (interm. 11-a).
- 35 d) A mixture of intermediate (11-a) (0.0291 mol) and sodium borohydride (0.1455 mol) in 1,4-dioxane (50ml) was cooled till 0°C under nitrogen. Acetic acid (0.1455 mol) in 1,4-dioxane (20ml) was added dropwise and the mixture was stirred and refluxed for 2 hours 30 min. The mixture was evaporated till dryness. Water was added to the residue.

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- The mixture was acidified with concentrated HCl and stirred for 30 min. The mixture was basified with a 50% NaOH solution and extracted with dichloromethane. The organic layer was dried, filtered off and evaporated till dryness. The residue was converted into the hydrochloric acid salt and then liberated. The residue (2.9g) was
- 5 purified by column chromatography over silica gel (eluent : CH₂Cl₂/CH₃OH 9.75/0.25). The pure fractions were collected and evaporated, yielding 2.4g (39%) (±)-3,4-dihydro-2H-naphtho[1,2-b]pyran-2-methanamine (interm. 12-a).
- In a similar manner was also prepared :
- (±)-3,4,7,8,9,10-hexahydro-2H-naphtho[1,2-b]pyran-2-methanamine (interm. 13-a).

10

Example 3-a

- A mixture of intermediate (5-a) (0.03mol) and benzenemethanamine (0.073mol) in 2,2'-oxybispropane (250ml) and N,N-dimethylacetamide (10ml) was hydrogenated with
- 15 palladium on activated carbon (10%) (1g) as a catalyst. After uptake of hydrogen (1 eq.), the catalyst was filtered off. The filtrate was evaporated. The residue was stirred in a mixture of water and 1,1'-oxybisethane. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated, yielding 6.5g of (±)-2,3,4,7,8,9-hexahydro-N-(phenylmethyl)cyclopenta[h]-1-benzopyran-2-methanamine (interm. 14-a).

20 Example 4-a

- A mixture of intermediate (14-a) (0.02mol) and 2-propenenitrile (0.2mol) in ethanol (100ml) was stirred and refluxed overnight. The solvent was evaporated. The residue was dissolved in methanol. Palladium on activated carbon (10%) (2g) was added and the mixture was hydrogenated. After uptake of hydrogen (3 eq.), the catalyst was filtered off
- 25 and the filtrate was evaporated, yielding 5.2g of (±)-N-[(2,3,4,7,8,9-hexahydrocyclopenta[h]-1-benzopyran-2-yl)methyl]-1,3-propanediamine (interm. 15-a).

Example 5-a

- A solution of ethyl 6-oxo-2,3-dimethyl-6H-furo[3,2-h][1]benzopyran-8-carboxylate (0.1 mol) in methanol (250 ml) was hydrogenated for 10 hours at 170 °C (pressurized)
- 30 with palladium on activated carbon , palladium content 5% (2 g) as a catalyst in the presence of a 4% thiophene solution (10 ml). After uptake of hydrogen (3 equiv), the catalyst was filtered off and the filtrate was evaporated. The residue was purified by flash column chromatography over silica gel (eluent: CH₂Cl₂). The desired fractions were
- 35 collected and the solvent was evaporated, yielding 20 g (72.9%) of (±)-ethyl 7,8-dihydro-2,3-dimethyl-6H-furo[3,2-h][1]benzopyran-8-carboxylate (interm. 16-a).

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Example 6-a

A mixture of intermediate (8-a) (6.9 g impure solid) and *N*-2-pyrimidinyl-1,2-propanediamine (0.02 mol) in methanol (200 ml) was hydrogenated with palladium on activated carbon (10%) (2 g) as a catalyst in the presence of a solution of thiophene (4%) (1 ml).

- 5 After uptake of hydrogen (1 eq.), the catalyst was filtered off. The filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/(CH₃OH/NH₃) 95/5). The pure fractions were collected and the solvent was evaporated. The residue was dissolved in 2-propanone and converted into the ethanedioic acid salt (1:2). The salt was filtered off and dried (vacuum; 60 °C), yielding 7.8 g
- 10 (73.0%) of (±)-*N*-[(2,3,4,7,8,9-hexahydrobenzo[2,1-*b*:3,4-*b'*]dipyran-2-yl)methyl]-*N'*-2-pyrimidinyl-1,3-propanediamine ethanedioate (1:2); mp. 190.4°C (comp. 1-a).

Example 7-a

A mixture of intermediate (13-a) (0.0088 mol) and 3-(2-pyrimidinylamino)propanal (0.0112 mol) in methanol (100ml) was hydrogenated with palladium on activated carbon (10%) (1g) as a catalyst at room temperature and 3 atm. in a Parr apparatus. After uptake of hydrogen (1eq.), the catalyst was filtered off and the filtrate was evaporated till dryness. The residue was purified by column chromatography over silica gel (eluent : CH₂Cl₂/(CH₃OH/NH₃) 97/3). The almost pure fractions were collected and evaporated.

20 The residue was purified again by HPLC over silica gel (eluent : CH₂Cl₂/(CH₃OH/NH₃) 95/5). The pure fractions were collected and evaporated, yielding 0.85g (27%) of (±)-*N*-[(3,4,7,8,9,10-hexahydro-2*H*-naphtho[1,2-*b*]pyran-2-yl)methyl]-*N'*-2-pyrimidinyl-1,3-propanediamine; mp. 57.6°C (comp. 5-a).

25 Example 8-a

- Intermediate 16-a (0.072 mol) was dissolved in methylbenzene (250 ml)/H (100 ml). The solution was cooled to -70 °C. Diisobutylaluminium hydride, 1.5M solution in hexane (0.1 mol) was added dropwise and the mixture was stirred for 1 hour at -70 °C. Methanol (15 ml) was added dropwise and the reaction mixture was allowed to warm to room temperature. The mixture was poured out into water, acidified with hydrochloric acid and extracted with diethyl ether. The separated organic layer was dried, filtered and the solvent evaporated. The residue was dissolved in methanol (150 ml). *N*-2-pyrimidinyl-1,3-propanediamine (0.06 mol) was added and the mixture was hydrogenated with palladium-on-charcoal (small amount) as a catalyst in the presence of thiophene, 4% solution (10 ml). After uptake of H₂ (1 equiv), the catalyst was filtered off and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 90/10). Three fraction groups were collected and the solvent was evaporated, yielding residues (1), (2) and (3) (12g). A sample of
- 35

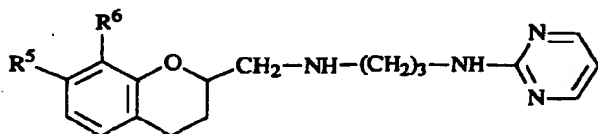
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residue (3) (3.6g) was dissolved in 2-propanone and converted into the ethanedioic acid salt (1:2) with a solution of ethanedioic acid.H₂O (0.020 mol) in 2-propanone. The precipitate was filtered off and dried, yielding 4.5 g (46.1%) of (±)-N-[(7,8-dihydro-2,3-dimethyl-6H-furo[3,2-h][1]benzopyran-8-yl)methyl]-N'-2-pyrimidinyl-1,3-propanediamine ethanedioate(1:2); mp. 208.8°C (comp. 7-a).

Residue (2) was repurified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 85/15). The desired fractions were collected and the solvent was evaporated. The residue (1.8 g) was dissolved in ethanol and converted into the ethanedioic acid salt (1:2) with ethanedioic acid (0.010 mol). The precipitate was filtered off and dried, yielding 1.1 g (3.3%) (±)-N-2-pyrimidinyl-N'-[(3,6,7,8-tetrahydro-2,3-dimethyl-2H-furo[3,2-h][1]benzopyran-8-yl)methyl]-1,3-propanediamine ethanedioate(1:2); mp. 171.2°C (comp. 8-a).

The following compounds were prepared :

Table 2-a



Co. No.	Ex. No.	R ⁵ , R ⁶	Physical data
1-a	6-a	-CH ₂ -CH ₂ -CH ₂ -O-	mp. 190.4°C/ . 2 (COOH) ₂
2-a	6-a	-CH ₂ -CH ₂ -CH ₂ -	mp. 118.2°C/ . 2 HCl . 1/2 H ₂ O
3-a	6-a	-O-CH ₂ -CH ₂ -O-	mp. 199.0°C/ . 2 (COOH) ₂
4-a	6-a	-O-CH ₂ -CH ₂ -CH ₂ -	mp. 197.6°C/ . 2 (COOH) ₂ . H ₂ O
5-a	7-a	-CH ₂ -CH ₂ -CH ₂ -CH ₂ -	mp. 57.6°C
6-a	7-a	-CH=CH-CH=CH-	mp. 226.3°C/ . (COOH) ₂
7-a	8-a	-C(CH ₃)=C(CH ₃)-O-	mp. 208.8°C/ . (COOH) ₂
8-a	8-a	-CH(CH ₃)-CH(CH ₃)-O-	mp. 171.2°C/ . (COOH) ₂
16-a	6-a	-O-CH ₂ -O-	mp. 169.3°C/ . 2 (COOH) ₂ . 1/2H ₂ O

Example 9-a

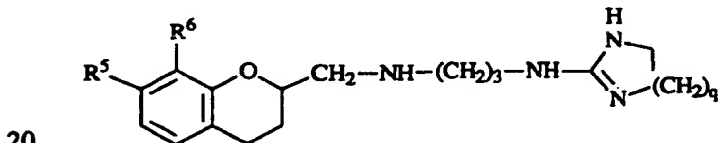
A mixture of intermediate (15-a) (0.02mol) and 2-methylthioimidazole monohydrochloride (0.02mol) in ethanol (100ml) was stirred and refluxed for 16 hours. The solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/(CH₃OH/NH₃) 90/9/1). The pure fractions were collected and

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- the solvent was evaporated. The residue was dissolved in 2-propanol and converted into the hydrochloric acid salt (1:2) with HCl/2-propanol. The salt was filtered off and dried, yielding 2.4g of (±)-N-(4,5-dihydro-1H-imidazol-2-yl)-N'-[(2,3,4,7,8,9-hexahydro-cyclopenta[h]-1-benzopyran-2-yl)methyl]-1,3-propanediamine dihydrochloride hemihydrate; mp. 189.7°C (comp. 9-a).

Example 10-a

- A mixture of compound (1-a) (0.0099 mol) in methanol (300 ml) was hydrogenated with palladium on activated carbon (10%) (2g) as a catalyst in the presence of a solution of thiophene (4%) (1 ml). After uptake of hydrogen (2 eq.), the catalyst was filtered off. The filtrate was evaporated and the residue was crystallized from methanol. The precipitate was filtered off and dried. This fraction was recrystallized from methanol. The precipitate was filtered off and dried, yielding 0.9 g (16.9%). The mother liquor was evaporated. The residue was dried, yielding 0.4 g (7.5%) (±)-N-[(2,3,4,7,8,9-hexahydrobenzo[2,1-b:3,4-b']dipyran-2-yl)methyl]-N'-(1,4,5,6-tetrahydro-2-pyrimidinyl)-1,3-propanediamine ethanedioate (1:2); mp. 226.9°C (comp. 10-a).

Table 2-a

Co. No.	Ex. No.	R ⁵ , R ⁶	q	Physical data
9-a	9-a	-CH ₂ -CH ₂ -CH ₂ -	1	mp. 189.7°C/ . 2 HCl . 1/2 H ₂ O
10-a	10-a	-CH ₂ -CH ₂ -CH ₂ -O-	2	mp. 226.9°C/ . 2 (COOH) ₂
11-a	10-a	-CH ₂ -CH ₂ -CH ₂ -	2	mp. 210.0°C/ . 2 HCl
12-a	10-a	-O-CH ₂ -CH ₂ -O-	2	mp. 209.1°C/ . 2 (COOH) ₂
13-a	10-a	-CH ₂ -CH ₂ -CH ₂ -CH ₂ -	2	. 2 HCl . 2 H ₂ O
14-a	10-a	-C(CH ₃)=C(CH ₃)-O	2	mp. 210.9°C/ . 2 (COOH) ₂
15-a	10-a	-CH(CH ₃)=CH(CH ₃)-O	2	mp. 206.4°C/ . 2 (COOH) ₂
17-a	10-a	-O-CH ₂ -O-	2	mp. 199.1°C/ . 2 (COOH) ₂

B. Preparation of compounds of formula (I) wherein R⁵ and R⁶ designate R^{5b} and R^{6b} and the intermediates thereof

Example 1-b

- a) 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol (0.093mol) was dissolved in

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acetic acid (100ml). Iodine monochloride (0.150mol) was warmed to 35°C and added as a fluid to the solution of 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol in acetic acid. The reaction mixture was stirred and refluxed for 24h. The mixture was cooled, poured out onto ice (200ml) and this mixture was extracted with CH₂Cl₂. The separated organic layer was dried, filtered and evaporated. The residue was purified by flash column chromatography over silica gel (eluent: CH₂Cl₂). The desired fractions were collected and the solvent was evaporated, yielding: 23.6g (72.2%) of (±)-6-fluoro-3,4-dihydro-8-iodo-2H-1-benzopyran-2-methanol acetate(ester) (interm. 1-b).

b) Intermediate 1-b (0.035 mol) was dissolved in N,N-diethylethanamine (250 ml). N₂ was allowed to bubble through the solution during 15 min. Bis(triphenylphosphine)-palladium (II) chloride (0.00042 mol) and cuprous iodide (0.0015 mol) were added. Trimethylsilylacetylene (0.056 mol) was added and the reaction mixture was stirred for 30 min at 50 °C (under N₂ flow). The blackened mixture was cooled and the solvent was evaporated. The residue was dissolved in methanol saturated with ammonia (50 ml) and stirred for 4 hours at room temperature. The solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 97/3). The desired fractions (mixture of several compounds) were collected and the solvent was evaporated. The residue (7.1 g) was dissolved in dichloromethane (150 ml). N,N-diethylethanamine (15 ml) was added, followed by 4-methylbenzenesulfonyl chloride (0.035 mol) and the reaction mixture was stirred overnight at room temperature. Water (150 ml) was added. The organic layer was separated. The aqueous layer was washed with CH₂Cl₂ (150 ml). The combined organic layers were dried (MgSO₄), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂). The pure fractions were collected and the solvent was evaporated, yielding 7.16 g (56.8%). This fraction was recrystallized from DIPE. The precipitate was filtered off and dried, yielding 4.27 g (33.9%) of (±)-8-ethynyl-6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol 4-methylbenzenesulfonate(ester); mp. 120.2°C (interm. 2-b).

In a similar manner was also prepared :

(±)-methyl 3-[6-fluoro-3,4-dihydro-2-[[[(4-methylphenyl)sulfonyl]oxy]methyl]-2H-1-benzopyran-8-yl]-2-propenoate (interm. 3-b).

Example 2-b

A suspension of (±)-methyl 6-fluoro-3,4-dihydro-8-iodo-2H-1-benzopyran-2-carboxylate (0.026mol), (trifluoromethyl)trimethylsilane (0.081mol), cuprous iodide (0.1mol) and kalium fluoride (0.081mol) in a mixture of DMF (50ml) and 1-methyl-2-pyrrolidinone (50ml) was stirred for 3h at 60°C. The cooled reaction mixture was poured

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out into a solution of iron (III) chloride (200g) and hydrochloric acid (50ml) in water (300ml). This mixture was extracted three times with diethyl ether (150ml). The combined organic layers were washed with a 5% aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution (decolorization), dried (MgSO_4), filtered and the solvent was evaporated. The residue was purified by flash column chromatography over silica gel (eluent: CH_2Cl_2). The pure fractions were collected and the solvent was evaporated, yielding 5.7g (78.8%). This fraction was recrystallized from DIPE. The precipitate was filtered off and dried, yielding 1.2g (16.6%) (\pm)-methyl 6-fluoro-3,4-dihydro-8-(trifluoromethyl)-2H-1-benzopyran-2-carboxylate; mp. 71.8°C (interm 4-b).

10

Example 3-b

a) A solution of intermediate 1-b (0.022 mol), 2-tributylstannyl furan (0.024 mol) and tetrakis(triphenylphosphine)palladium (0.0005 mol) in 1-methyl-2-pyrrolidinone (50 ml) was stirred for 16 hours at 100 °C. The cooled reaction mixture was poured out into water (200 ml) and this mixture was extracted with DIPE (200 ml). The separated organic layer was dried, filtered and the solvent was evaporated. The residue was stirred in methanol saturated with ammonia (50 ml) for 16 hours. The solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2 /hexane 50/50, upgrading to pure CH_2Cl_2). The desired fractions were collected and the solvent was evaporated, yielding 4.5 g (82.4%) of (\pm)-6-fluoro-8-(2-furanyl)-3,4-dihydro-2H-1-benzopyran-2-methanol (interm. 5-b).

b) 4-methylbenzenesulfonyl chloride (0.021 mol) was added to a solution of intermediate 5-b (0.018 mol) in CH_2Cl_2 (50 ml). *N,N*-diethylethanamine (5 ml) was added and the reaction mixture was stirred for 24 hours at room temperature. The reaction mixture was poured out into water and this mixture was extracted with CH_2Cl_2 . The separated organic layer was dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2 /hexane 50/50). The pure fractions were collected and the solvent was evaporated. The residue was stirred in DIPE and the white precipitate was filtered off and dried, yielding: 5.2 g (71.8%) of (\pm)-6-fluoro-8-(2-furanyl)-3,4-dihydro-2H-1-benzopyran-2-methanol 4-methylbenzenesulfonate(ester); mp. 110.4°C (interm. 6-b).

In a similar manner were also prepared :

(\pm)-6-fluoro-3,4-dihydro-8-(2-thienyl)-2H-1-benzopyran-2-methanol 4-methylbenzenesulfonate(ester) (interm. 7-b);

(\pm)-6-fluoro-3,4-dihydro-8-phenyl-2H-1-benzopyran-2-methanol 4-methylbenzenesulfonate(ester) (interm. 8-b);

(\pm)-6-fluoro-3,4-dihydro-8-(2-pyridinyl)-2H-1-benzopyran-2-methanol 4-methyl-

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- benzenesulfonate(ester) (interm. 9-b);
(±)-8-(ethylthio)-6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol
methanesulfonate(ester) ; mp. 107,7°C (interm. 10-b); and
(±)-6-fluoro-3,4-dihydro-8-(phenylthio)-2H-1-benzopyran-2-methanol
5 methanesulfonate(ester) (interm. 11-b).

Example 4-b

- A solution of intermediate 11-b (0.016 mol) in dichloromethane (15 ml) was added dropwise to a mixture of Al₂O₃ (16 g; neutral, wet) and 2 KHSO₅.KHSO₄.K₂SO₄
10 (0.016 mol) in dichloromethane (65 ml). The reaction mixture was stirred overnight at room temperature. The reaction mixture was filtered, washed with CH₂Cl₂ and the filtrate was dried (MgSO₄), filtered and the solvent evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 97.5/2.5). The desired fractions were collected and the solvent was evaporated. The residue (7.2 g) was
15 repurified by column chromatography over silica gel (eluent: CH₂Cl₂, upgrading to CH₂Cl₂/(CH₃OH/NH₃) 50/50). The pure fractions were collected and the solvent was evaporated, yielding 3.8 g (61.8%) of (±)-6-fluoro-3,4-dihydro-8-(phenylsulfinyl)-2H-1-benzopyran-2-methanol methanesulfonate(ester) (interm. 12-b).

20 Example 5-b

- a) (±)-Methyl 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxylate (0.26mol) was added to stirred nitric acid (300ml). The reaction mixture was stirred for 10 min at 40°C. The reaction mixture was stirred for 60 min at 60°C. The mixture was poured out into water. The resulting precipitate was filtered off. The filtrate was extracted with CH₂Cl₂.
25 The separated organic layer was evaporated, leaving 33g of residue, yielding 33g of (±)-6-fluoro-3,4-dihydro-8-nitro-2H-1-benzopyran-2-carboxylic acid (interm. 13-b).
b) A 1M solution of (CH₃)₂S.BH₃ in dichloromethane (0.28mol) was added dropwise to a mixture of intermediate 13-b (0.25mol) in tetrahydrofuran (800ml), stirred under N₂ flow. About 60ml of the solvent was removed by distillation. The reaction mixture was
30 stirred and refluxed for 2h. The mixture was cooled, decomposed with CH₃OH (20ml), poured out into H₂O/NaOH and this mixture was extracted with CH₂Cl₂. The separated organic layer was washed with water, dried (MgSO₄), filtered and the solvent was evaporated, yielding 59g of (±)-6-fluoro-3,4-dihydro-8-nitro-2H-1-benzopyran-2-methanol (104% crude residue) (interm. 14-b).
35 c) A mixture of intermediate 14-b (0.25mol), 3,4-dihydro-2H-pyran (0.50mol) and hydrochloric acid in 2-propanol (0.5ml) in trichloromethane (700ml) was stirred for 3h on a water bath. The reaction mixture was washed with a 10% NaOH solution. The

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organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated, yielding 81g of (±)-6-fluoro-3,4-dihydro-8-nitro-2-[[[(tetrahydro-2H-pyran-2-yl)oxy]methyl]-2H-1-benzopyran (104% crude residue) (interm. 15-b).

- d) A mixture of intermediate 15-b (0.47mol) in methanol (600ml) was hydrogenated
5 with palladium on activated carbon, palladium content 10% (5g) as a catalyst in the presence of a 4% thiophene solution (3ml). After uptake of H₂ (3 equiv), the catalyst was filtered off and the filtrate was evaporated, yielding 130g (98.3%) of (±)-6-fluoro-3,4-dihydro-2-[[[(tetrahydro-2H-pyran-2-yl)oxy]methyl]-2H-1-benzopyran-8-amine (interm. 16-b).
- 10 e) A mixture of intermediate 16-b (0.036 mol), 2,5-dimethoxytetrahydrofuran (0.22 mol) and PTSA (catalytic quantity) in DMF (140 ml) was stirred for 90 min at 100 °C. The solvent was evaporated. The residue was dissolved in CH₂Cl₂. The organic solution was washed once with water, dried (MgSO₄), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂).
15 The pure fractions were collected and the solvent was evaporated, yielding 6.6 g (55.3%) of (±)-6-fluoro-3,4-dihydro-8-(1H-pyrrol-1-yl)-2-[[[(tetrahydro-2H-pyran-2-yl)oxy]methyl]-2H-1-benzopyran (interm. 17-b).
- f) A hydrochloric acid solution 10% (25 ml) was added to a mixture of intermediate 17-b (0.019 mol) in methanol (65 ml). The reaction mixture was stirred for 60 min at room
20 temperature. The solvent was evaporated. The residue was partitioned between CH₂Cl₂ and H₂O. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH₂Cl₂/CH₃OH 98/2). The pure fractions were collected and the solvent was evaporated, yielding: 3.4 g (72.4%) of (±)-6-fluoro-3,4-dihydro-8-(1H-pyrrol-1-yl)-2H-1-benzopyran-2-methanol (interm. 18-b).
25 g) N,N-diethylethanamine (7 ml) was added dropwise to a mixture of intermediate 18-b (0.024 mol) and methanesulfonyl chloride (0.035 mol) in 2-propanone (30 ml), stirred and cooled on an ice bath. The reaction mixture was stirred for 1 hour. The mixture was filtered and the filtrate was evaporated. The residue was dissolved in CH₂Cl₂. The
30 organic solution was washed with an aqueous hydrochloric acid solution, dried (MgSO₄), filtered and the solvent was evaporated, yielding 7.6 g (97.3%) of (±)-6-fluoro-3,4-dihydro-8-(1H-pyrrol-1-yl)-2H-1-benzopyran-2-methanol methanesulfonate(ester) (interm. 19-b).

35 Example 6-b

A solution of Br₂ (0.01 mol) in dichloromethane (50 ml) was added dropwise to a solution of (±)-6-fluoro-3,4-dihydro-8-(2-thienyl)-2H-1-benzopyran-2-methanol 4-

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methylbenzenesulfonate(ester) (0.01 mol) in dichloromethane (50 ml), stirred at 0 °C. The reaction mixture was poured out into water. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was crystallized from DIPE. The precipitate was filtered off and dried, yielding 3.8 g (76.4%) of (±)-8-(5-bromo-2-thienyl)-6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol 4-methylbenzene-sulfonate(ester) (interm. 20-b).

Example 7-b

Calcium oxide (5g) was added to a solution of intermediate 2-b (0.0125mol) and N-2-pyrimidinyl-1,3-propanediamine (0.019mol) in tetrahydrofuran (100ml) and the reaction mixture was stirred overnight at 150°C (pressure vessel). The reaction mixture was cooled and filtered. The filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent : CH₂Cl₂, upgrading to CH₂Cl₂/CH₃OH 90/10). Two desired fractions were collected and the solvent was evaporated, yielding 1.2g of the pure fraction. This fraction was dissolved in methanol (100ml) and converted into the ethanedioic acid salt (1:1) with ethanedioic acid hydrate (0.620g). The mixture was concentrated, 2-propanone was added and the resulting precipitate was filtered off and dried, yielding 1.2g (22.3%) of (±)-N-[(8-ethynyl-6-fluoro-3,4-dihydro-2H-1-benzopyran-2-yl)methyl]-N'-2-pyrimidinyl-1,3-propanediamine ethanedioate(1:1); mp. 201.1°C (comp. 1-b).

Example 8-b

A solution of diisobutylaluminum hydride in methylbenzene (20%) (22ml) was added dropwise to a solution of intermediate 4-b (0.018mol) in methylbenzene (50ml), stirred at -70°C. This mixture was stirred for 1 hour at -70°C. Methanol (10ml) was added and the mixture was warmed to room temperature, poured out into water, acidified with HCl, then extracted with dichloromethane. The separated organic layer was evaporated. A mixture of the residue and N-2-pyrimidinyl-1,3-propanediamine (0.014mol) was hydrogenated with palladium (2g) as a catalyst in the presence of a solution of thiophene (4%) (2ml). After uptake of hydrogen (250ml), the catalyst was filtered off and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/ CH₃OH 90/10). The pure fractions were collected and the solvent was evaporated. The residue (2.2g) was dissolved in ethanol (50ml) and converted into the ethanedioic acid salt (1:1) with ethanedioic acid (0.024mol). The precipitate was filtered off and dried. This fraction was recrystallized from methanol (±300ml). The precipitate was filtered off and dried, yielding 0.950g (13.6%) of (±)-N-[[6-fluoro-3,4-dihydro-8-(trifluoromethyl)-2H-1-benzopyran-2-yl)methyl]-N'-2-pyrimidinyl-1,3-

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propanediamine ethanedioate (1:1); mp. 216.3°C (comp. 2-b).

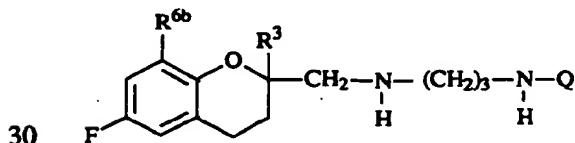
Example 9-b

- A solution of the free base of compound (2-b) (0.00313mol) and ethanedioic acid dihydrate (0.00635mol) in methanol (50ml) was hydrogenated for 2 hours at 50°C, with
 5 palladium on activated carbon (1g) as a catalyst. After uptake of hydrogen (2 eq.), the catalyst was filtered off and the filtrate was concentrated. The resulting precipitate was filtered (*) off and dried, yielding 0.310 g (17.2%) of product. The corresponding (*) filtrate was treated with 2-propanone and the resulting precipitate was filtered off and
 10 dried, yielding 0.500 g (27.7%) of (±)-N-[[[6-fluoro-3,4-dihydro-8-(trifluoromethyl)-2H-1-benzopyran-2-yl]methyl]-N'-(1,4,5,6-tetrahydro-2-pyrimidinyl)-1,3-propanediamine ethanedioate (1:2). hemihydrate; mp. 177.1°C (comp. 3-b).

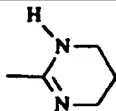
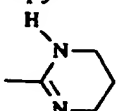
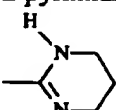
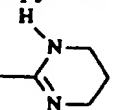
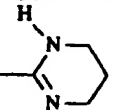
Example 10-b

- Reaction under N₂ flow. A solution of Bu₃SnSCH₂COOEt (0.011 mol) in methyl-
 15 benzene (40 ml) was added dropwise to a mixture of intermediate 1-b (0.011 mol) and tetrakis(triphenylphosphine)palladium (0.00029 mol) in methylbenzene (160 ml). The reaction mixture was stirred and refluxed overnight. The reaction mixture was cooled, washed with a 10% KF solution, dried (MgSO₄), filtered and the solvent was
 20 evaporated. The residue was purified over silica gel on a glass filter (eluent: CH₂Cl₂/(CH₃OH/NH₃) 95/5). The desired fractions were collected and the solvent was evaporated. The residue was dissolved in 2-propanone and converted into the ethanedioic acid salt (1:2). The precipitate was filtered off and dried (vacuum; 60 °C), yielding 4.4g (65.1%) of (±)-ethyl [[6-fluoro-3,4-dihydro-2-[[[3-(2-pyrimidinylamino)propyl]-amino]methyl]-2H-1-benzopyran-8-yl]thio]acetate ethanedioate(1:2); mp. 154.4°C
 25 (compound 17-b).

Table 1-b



Co. No.	Ex. No.	R ^{6b}	Q	Physical data
1-b	1-b	-C≡CH	2-pyrimidinyl	mp. 201.1°C/.(COOH) ₂
2-b	2-b	-CF ₃	2-pyrimidinyl	mp. 216.3°C/.(COOH) ₂

Co. No.	Ex. No.	R ^{6b}	Q	Physical data
3-b	3-b	-CF ₃		mp. 177.1°C/ .2 (COOH) ₂ . 1/2 H ₂ O
4-b	1-b	-CH=CH-C(=O)OCH ₃	2-pyrimidinyl	(E) .2 (COOH) ₂
5-b	1-b	2-furanyl	2-pyrimidinyl	mp. 192.8°C/ .2 (COOH) ₂
6-b	1-b	2-thienyl	2-pyrimidinyl	mp. 205.8°C/ .3/2 (COOH) ₂
7-b	3-b	2-thienyl		mp. 216.8°C/ .2 (COOH) ₂
8-b	1-b	5-bromo-2-thienyl	2-pyrimidinyl	mp. 191.5°C/ .2 (COOH) ₂
9-b	3-b	-(CH ₂) ₂ -C(O)-OCH ₃		mp. 209.6°C/ .2 (COOH) ₂
10-b	1-b	phenyl	2-pyrimidinyl	mp. 159.2°C/ .2 (COOH) ₂
11-b	1-b	2-pyridinyl	2-pyrimidinyl	mp. 158.9°C/ (E)-2-butenedioate (1:1)
12-b	1-b	-S-CH ₂ -CH ₃	2-pyrimidinyl	mp. 160.6°C/ 2 (COOH) ₂
13-b	1-b	phenylthio	2-pyrimidinyl	mp. 181.0°C/ 2 (COOH) ₂
14-b	1-b	phenylsulfinyl	2-pyrimidinyl	mp. 129.4°C/ 2 (COOH) ₂
15-b	1-b	1H-pyrrol-1-yl	2-pyrimidinyl	mp. 162.1°C/ 2 (COOH) ₂
16-b	3-b	1H-pyrrol-1-yl		mp. 177.7°C/ .2 (COOH) ₂
17-b	4-b	-S-CH ₂ -C(=O)-O-CH ₂ CH ₃	2-pyrimidinyl	mp. 154.4°C/ 2 (COOH) ₂
18-b	3-b	2-pyridinyl		mp. 186.3°C/ .2 (COOH) ₂

C. Preparation of the compounds of formula (I) wherein R⁵ and R⁶ designate R^{5c} and R^{6c} and the intermediates thereof.

5 Example 1-c

A mixture of 3,6-dichloropyridazine (0.168mol), 1,3-propanediamine (0.84mol) and sodium carbonate (0.17mol) in ethanol (500ml) was stirred and refluxed overnight. The

-30-

reaction mixture was filtered over dicalite. The filtrate was evaporated. The residue was crystallized from acetonitrile. The crystals were filtered off and dried, yielding 20.7 g of N-(6-chloro-3-pyridazinyl)-1,3-propanediamine; mp. 124.9°C (interm. 1-c).

In a similar manner were also prepared :

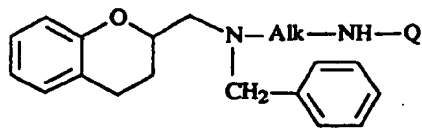
- 5 N-3-pyridazinyl-1,3-propanediamine dihydrochloride; mp. 210.9°C (interm. 2-c).
N-(6-methyl-3-pyridazinyl)-1,3-propanediamine (interm. 3-c).

Example 2-c

- 10 a) A mixture of (\pm)-3-[[[(3,4-dihydro-2H-1-benzopyran-2-yl)methyl](phenylmethyl)-amino]propanenitrile (0.069mol) in methanol (250ml) was hydrogenated with Raney nickel (5g) as a catalyst. After uptake of hydrogen (2 eq.), the catalyst was filtered off and the filtrate was evaporated, yielding 20g (94% crude residue) of (\pm)-N-[[[(3,4-dihydro-2H-1-benzopyran-2-yl)methyl]-N-(phenylmethyl)-1,3-propanediamine (interm. 4-c).
- 15 b) A mixture of intermediate (4-c) (0.01mol) and 2-methylthio-4(1H)-pyrimidinone (0.01mol) was heated for 2 hours at 150°C. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 95/5). The pure fractions were collected and the solvent was evaporated. The residue was converted into the
- 20 hydrochloric acid salt (1:2) with HCl/2-propanol and crystallized from 1,1'-oxybis-ethane. The salt was filtered off and dried, yielding 2.8g (56.5%) of (\pm)-2-[[[3-[[[(3,4-dihydro-2H-1-benzopyran-2-yl)methyl](phenylmethyl)amino]propyl]amino]-4(1H)-pyrimidinone dihydrochloride monohydrate; mp. 150.2°C (interm. 5-c).

In a similar manner were prepared :

25 Table 1-c



Int. No.	Alk	Q	Physical data
5-c	-(CH ₂) ₃ -	4-hydroxy-2-pyrimidinyl	mp. 150.2°C/ .2HCl.H ₂ O
6-c	-(CH ₂) ₂ -	4-hydroxy-6-methyl-2-pyrimidinyl	mp. 212.1°C/ .2HCl
7-c	-(CH ₂) ₂ -	4-hydroxy-6-propyl-2-pyrimidinyl	mp. 190.5°C/ .2HCl
8-c	-(CH ₂) ₃ -	2-pyrazinyl	-
9-c	-(CH ₂) ₃ -	5-chloro-2-pyridinyl	mp. 111.3°C/ .2HCl.1/2H ₂ O
10-c	-(CH ₂) ₃ -	2-chloro-4-pyrimidinyl	-

Int. No.	Alk	Q	Physical data
11-c	-(CH ₂) ₃ -	2-methoxy-4-pyrimidinyl	-
12-c	-(CH ₂) ₃ -	2-(dimethylamino)-4-pyrimidinyl	-
13-c	-(CH ₂) ₃ -	2-(1-piperidinyl)-4-pyrimidinyl	-
14-c	-(CH ₂) ₃ -	2-(methylamino)-4-pyrimidinyl	-

Example 3-c

- a) A mixture of 2-chlorocarbonyl-3,4-dihydro-2H-1-benzopyran (0.47 mol) in **5** *N,N*-dimethylacetamide (100ml), a solution of thiophene (4%) (3ml) and 2,2'-oxybispropane (400ml) was hydrogenated with palladium on activated carbon (10%) (5g) as a catalyst. After uptake of hydrogen (1 eq.), the catalyst was filtered off and the filtrate was evaporated. The residue, potassium acetate (20g) and benzenemethanamine (50g) in *N,N*-dimethylacetamide (2ml) and methanol (300ml) was hydrogenated with palladium **10** on activated carbon (10%) (5g) as a catalyst. After uptake of hydrogen (1 eq.), the catalyst was filtered off and the filtrate was evaporated. The residue in methanol (500ml) was hydrogenated with palladium on activated carbon (10%) (5g) as a catalyst. After uptake of hydrogen (1 eq.), the catalyst was filtered off and the filtrate was evaporated. The residue was taken up in 1,1'-oxybisethane and washed with a NaOH-solution. The **15** organic layer was dried (MgSO₄), filtered off and evaporated. The residue (70g) was distilled at 70°C (0.1mm Hg), yielding 48.7g (63.5%) of (±)-3,4-dihydro-2H-1-benzopyran-2-methanamine (interm. 15-c).
- b) A mixture of intermediate (15-c) (0.12mol) and 2-propenenitrile (0.12mol) in ethanol (235ml) was stirred and refluxed for 4 hours. The solvent was evaporated, yielding 27g **20** crude residue of (±)-3-[[[(3,4-dihydro-2H-1-benzopyran-2-yl)methyl]amino]propane-nitrile (interm. 16-c).
- c) A mixture of intermediate (16-c) (0.12mol) in methanol saturated with ammonia (500ml) was hydrogenated with Raney nickel (6g) as a catalyst. After uptake of hydrogen (2 eq.), the catalyst was filtered off and the filtrate was evaporated. The **25** residue was purified by distillation, yielding 24g (90.8%) of (±)-*N*-[(3,4-dihydro-2H-1-benzopyran-2-yl)methyl]-1,3-propanediamine (interm. 17-c).

B. Preparation of the final compounds (-c)**Example 4-c**

- 30** A mixture of intermediate (1-c) (0.058 mol), 3,4-dihydro-2H-1-benzopyran-2-carboxaldehyde (0.064 mol) and potassium acetate (7.1 g) in methanol (200 ml) was

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hydrogenated with platinum on activated carbon 5% (2 g) as a catalyst in the presence of a solution of thiophene (4%) (1 ml). After uptake of hydrogen (1 eq.), the catalyst was filtered off. The filtrate was evaporated. The residue was dissolved in H_2O/CH_2Cl_2 and alkalized with NaOH. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 90/10). Two fractions were collected. The first fraction was evaporated. The residue was crystallized from 2-propanol. The crystals were filtered off and dried. The second fraction was evaporated and the residue was crystallized from 2-propanol. The crystals were filtered off and dried, yielding 3.09 g (16%) of (\pm)-N-(6-chloro-3-pyridazinyl)-N'-[(3,4-dihydro-2H-1-benzopyran-2-yl)methyl]-1,3-propanediamine; mp. 107.8°C (comp. 1-c).

Example 5-c

Intermediate (5-c) (0.005mol) was hydrogenated in methanol (250ml) with palladium on activated carbon (2g) as a catalyst. After uptake of hydrogen (1 eq.), the catalyst was filtered off. The solvent was evaporated. The residue (2g) was recrystallized from methanol. The crystals were filtered off and dried, yielding 0.7g (36%) of (\pm)-2-[[3-[[[(3,4-dihydro-2H-1-benzopyran-2-yl)methyl]amino]propyl]amino]-4(1H)-pyrimidinone dihydrochloride (comp. 8-c).

Example 6-c

A mixture of intermediate (17-c) (0.03mol) and 2-methylthio-4(1H)-pyrimidinone (0.03mol) in 2-methoxyethanol (50ml) was stirred and refluxed overnight. The solvent was evaporated. The residue was stirred in water and extracted with dichloromethane. The separated organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/(CH_3OH/NH_3)$ 95/5). The pure fractions were collected and the solvent was evaporated. This fraction was dissolved in 2-propanone and converted into the ethanedioic acid salt (2:3). The salt was filtered off and crystallized from methanol. The solid (1.2g) was filtered off and dried, yielding 1.0g (7.4%) of (\pm)-2-[[3-[[[(3,4-dihydro-2H-1-benzopyran-2-yl)methyl]amino]propyl]amino]-4(3H)-pyrimidinone ethanedioate(2:3); mp. 206.7°C (comp. 9-c).

Example 7-c

A mixture of (\pm)-N²-[3-[[[(3,4-dihydro-2H-1-benzopyran-2-yl)methyl]amino]propyl]-N⁴,N⁴-dimethyl-2,4-pyrimidinediamine dihydrochloride (0.0067mol) in methanol (150ml) was hydrogenated with palladium on activated carbon 10% (2g) as a catalyst in

-33-

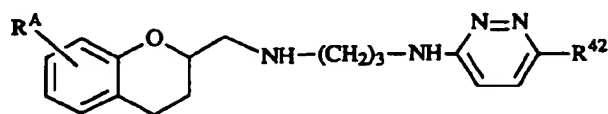
the presence of a solution of hydrochloric acid in 2-propanol (2ml). After uptake of hydrogen (2 eq.), the catalyst was filtered off. The filtrate was evaporated and the residue was crystallized twice from methanol. The crystals were filtered off and dried, yielding 0.32g (13.1%) of (±)-2-[[[3-[[[(3,4-dihydro-2H-1-benzopyran-2-yl)methyl]-amino]propyl]amino]-5,6-dihydro-4(3H)-pyrimidinone dihydrochloride; mp. 273.6°C (comp. 12-c).

Example 8-c

A mixture of compound (17-c) (0.02mol) in methanol (200ml) was hydrogenated with palladium on activated carbon 10% (2g) as a catalyst. After uptake of hydrogen (2 eq.), the catalyst was filtered off. The filtrate was evaporated. The residue was dissolved in 2-propanol and converted into the hydrochloric acid salt (1:2) with HCl/2-propanol. The salt was filtered off and dried, yielding 5.61g (75%) of (±)-N-[(3,4-dihydro-2H-1-benzopyran-2-yl)methyl]-N'-(3,4,5,6-tetrahydro-2-pyridinyl)-1,3-propanediamine dihydrochloride; mp. 211.1°C (comp. 15-c).

Example 9-c

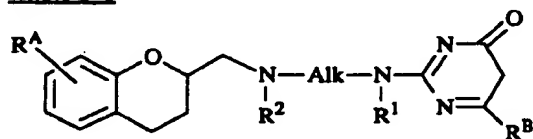
A mixture of the free base of compound (19-c) (0.0145mol) and Raney nickel (5g) in tetrahydrofuran (150ml) was stirred and refluxed for 1 hour. The catalyst was filtered off and the filtrate was evaporated. The residue was dissolved in 2-propanone and converted into the ethanedioic acid salt (1:2). The salt was filtered off (3g) and recrystallized from methanol (600ml). The crystals were filtered off and dried, yielding 2.5g (36.2%) of (±)-N-[(3,4-dihydro-2H-1-benzopyran-2-yl)methyl]-N'-4-pyrimidinyl-1,3-propanediamine ethanedioate(1:2); mp. 222.2°C (comp. 20-c).

Table 2-c

Co. No.	Ex. No.	R ^A	R ⁴²	Physical data
1-c	4-c	H	Cl	mp. 107.8°C
2-c	4-c	H	H	mp. 169.7°C .2HCl.1/2H ₂ O
3-c	4-c	H	CH ₃	mp. 158.7°C/ .2HCl.1/2H ₂ O

Co. No.	Ex. No.	R ^A	R ⁴²	Physical data
4-c	4-c	H	Cl	mp. 203.1°C/ [α] _D ²⁰ = -48.51° (c = 1% in methanol)/ (-)-(R).2HCl
5-c	4-c	6-F	Cl	mp. 229.3°C/ [α] _D ²⁰ = -27.00° (c = 1% in methanol)/ (-)-(R).2HCl
6-c	4-c	6-F	Cl	mp. 243.2°C/ [α] _D ²⁰ = +33.67° (c = 1% in methanol)/ (+)-(S).2HCl
7-c	6-c	7-CH ₂ -CH ₃	Cl	mp. 223.9°C/ .2HCl
25-c	4-c	8-OCH ₃	Cl	mp. 182.6°C/ .2HCl . H ₂ O
26-c	5-c	H	CN	mp. 192.3°C/ (COOH) ₂
27-c	5-c	H	OH	mp. 191.1°C/ (COOH) ₂
28-c	5-c	H	-C(=O)-NH ₂	mp. 211.7°C/ (COOH) ₂

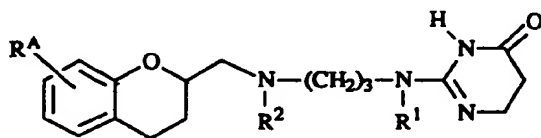
Table 3-c



5

Co. No.	Ex. No.	R ^A	R ²	R ¹	Alk	R ^B	Physical data
8-c	5-c	H	H	H	-(CH ₂) ₃ -	H	.2HCl
9-c	6-c	H	H	H	-(CH ₂) ₃ -	H	mp. 206.7°C/ .3/2 (COOH) ₂
10-c	6-c	H	H	H	-(CH ₂) ₂ -	(CH ₂) ₂ CH ₃	mp. 227.9°C/ .2HCl
11-c	6-c	H	H	H	-(CH ₂) ₂ -	H	mp. 227.6°C/ .2HCl

Table 4-c

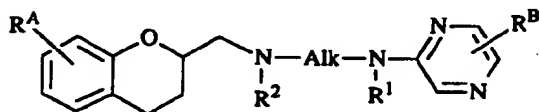


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Co.No	Ex. No.	R ^A	R ²	R ¹	Physical data
12-c	7-c	H	H	H	mp. 273.6°C/ .2HCl

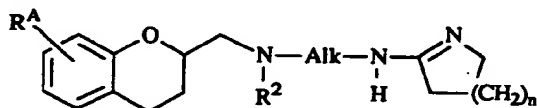
Table 5-c



5

Co. No.	Ex. No.	R ^A	R ²	R ¹	Alk	R ^B	Physical data
13-c	6-c	6-F	H	H	-(CH ₂) ₃ -	H	mp. 198.1°C/ .2HCl
14-c	5-c	H	H	H	-(CH ₂) ₃ -	H	mp. 188.9°C/ .2HCl

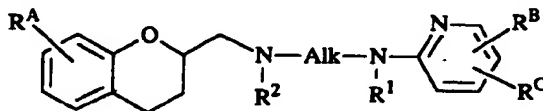
Table 6-c



10

Co. No.	Ex. No.	R ^A	R ²	Alk	R ^B	n	Physical data
15-c	8-c	H	H	-(CH ₂) ₃ -	H	2	mp. 211.1°C/ .2HCl

Table 7-c

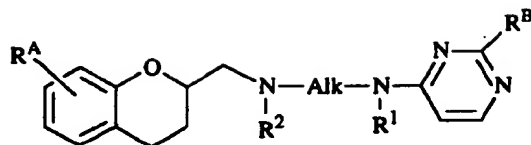


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Co. No.	Ex. No.	R ^A	R ²	Alk	R ¹	R ^B	R ^C	Physical data
16-c	4-c	H	H	-(CH ₂) ₃ -	H	H	H	mp. 182.6°C/ .2HCl
17-c	4-c	H	H	-(CH ₂) ₃ -	H	6-CH ₃	3-C(=O)NH ₂	mp. 246.9°C/ .2HCl.H ₂ O

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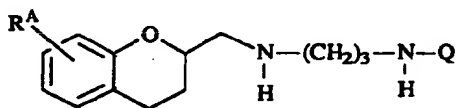
Table 8-c



Co. No.	Ex. No.	R ^A	R ²	R ¹	Alk	R ^B	Physical data
18-c	6-c	H	H	H	-(CH ₂) ₃ -	-S-CH ₃	mp. 225.8°C/ .2(COOH) ₂
19-c	10-c	H	H	H	-(CH ₂) ₃ -	H	mp. 222.2°C/ .2(COOH) ₂
20-c	10-c	H	CH ₂ CH ₃	H	-(CH ₂) ₃ -	H	mp. 117.4°C/ .2(COOH) ₂ .1/2 H ₂ O
21-c	5-c	H	H	H	-(CH ₂) ₃ -	-O-CH ₃	mp. 179.6°C/ .2(COOH) ₂
22-c	5-c	H	H	H	-(CH ₂) ₃ -	-N(CH ₃) ₂	mp. 204.6°C/ .2(COOH) ₂
23-c	5-c	H	H	H	-(CH ₂) ₃ -	1-piperidiny1	mp. 206.8°C/ .2(COOH) ₂
24-c	5-c	H	H	H	-(CH ₂) ₃ -	-NH-CH ₃	mp. 188.1°C/ .2(COOH) ₂

5

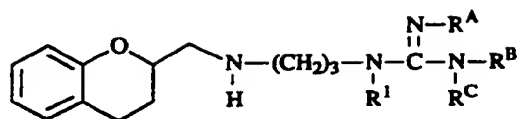
Table 9-c



Co. No.	Ex. No.	R ^A	Q	Physical data
29-c	6-c	6-F	2-thiazolyl	mp. 145.3°C/ .2 HCl
30-c	5-c	H		mp. 156.2°C
31-c	5-c	H		mp. 214.1°C
32-c	5-c	H		mp. 184.9°C/ (COOH) ₂
33-c	6-c	H		mp. 168.2°C

10

Table 10-c



5

Co. No.	Ex. No.	R ¹	R ^A	R ^B	R ^C	Physical data (mp in °C)/base/salt
34-c	6-c	H	CN	2-phenylethyl	methyl	159.4/ .2 (COOH) ₂
35-c	9-c	H	H	2-phenylethyl	methyl	198.5
36-c	6-c	H	CN	(2-methoxyphenyl)methyl	methyl	166.1/ (COOH) ₂
37-c	9-c	H	H	(2-methoxyphenyl)methyl	methyl	191.9/ 2 HCl
38-c	6-c	H	CN	4-methyl-1-piperazinyl		171.6
39-c	6-c	CH ₃	CN	phenylmethyl	methyl	142.9/ (COOH) ₂
40-c	9-c	H	H	cyclohexyl	H	242.5/ 2HCl
41-c	9-c	H	C(=O)NH ₂	cyclohexyl	H	201.5/ 2HCl

D. Pharmacological Example**Example 1-d**

- Segments of basilar arteries taken from pigs (anaesthetised with sodium pentobarbital) were mounted for recording of isometric tension in organ baths. The preparations were bathed in Krebs - Henseleit solution. The solution was kept at 37°C and gassed with a mixture of 95% O₂ - 5% CO₂. The preparations were stretched until a stable basal tension of 2 grams was obtained.
- The preparations were made to constrict with serotonin (3×10^{-7} M). The response to the addition of serotonin was measured and subsequently the serotonin was washed away. This procedure was repeated until stable responses were obtained.
- Subsequently the test compound was administered to the organ bath and the constriction of the preparation was measured. This constrictive response was expressed as a percentage of the response to serotonin as measured previously.
- The lowest active concentration was defined as the concentration at which 50% of the response to serotonin is obtained.

In table 3 the lowest active concentration of compounds of formula (I) are presented.

Table 1-d

Co. No.	Lowest active concentration (M)
1-a	$3 \cdot 10^{-8}$
2-a	$3 \cdot 10^{-7}$
4-a	$1 \cdot 10^{-6}$
5-a	$3 \cdot 10^{-7}$
9-a	$1 \cdot 10^{-8}$
10-a	$3 \cdot 10^{-9}$
11-a	$3 \cdot 10^{-8}$
12-a	$3 \cdot 10^{-8}$
13-a	$3 \cdot 10^{-7}$

5

Table 2-d

Co. No.	Lowest active concentration (M)
1-b	$1 \cdot 10^{-7}$
3-b	$3 \cdot 10^{-7}$
4-b	$3 \cdot 10^{-8}$
5-b	$3 \cdot 10^{-8}$
6-b	$1 \cdot 10^{-7}$
7-b	$3 \cdot 10^{-9}$

Table 3-d

Co. no.	Lowest active concentration (M)
1-c	$1 \cdot 10^{-6}$
3-c	$1 \cdot 10^{-7}$
4-c	$1 \cdot 10^{-7}$
5-c	$3 \cdot 10^{-7}$
12-c	$1 \cdot 10^{-6}$
13-c	$< 3 \cdot 10^{-7}$
14-c	$1 \cdot 10^{-7}$
15-c	$3 \cdot 10^{-8}$
16-c	$1 \cdot 10^{-6}$
18-c	$1 \cdot 10^{-7}$

Co. no.	Lowest active concentration (M)
19-c	$3 \cdot 10^{-7}$
21-c	$1 \cdot 10^{-7}$
22-c	$1 \cdot 10^{-6}$
23-c	$3 \cdot 10^{-7}$
24-c	$3 \cdot 10^{-8}$

E. Composition examples

- 5 "Active ingredient" (A.I.) as used throughout these examples relates to a compound of formula (I), a pharmaceutically acceptable acid addition salt or a stereochemically isomeric form thereof.

Example 1-c : ORAL DROPS

- 10 500 Grams of the A.I. was dissolved in 0.5 l of 2-hydroxypropanoic acid and 1.5 l of the polyethylene glycol at 60~80°C. After cooling to 30~40°C there were added 35 l of polyethylene glycol and the mixture was stirred well. Then there was added a solution of 1750 grams of sodium saccharin in 2.5 l of purified water and while stirring there were added 2.5 l of cocoa flavor and polyethylene glycol q.s. to a volume of 50 l, providing an oral drop solution comprising 10 mg/ml of A.I.. The resulting solution was filled into suitable containers.

15 Example 2-c : ORAL SOLUTION

- 9 Grams of methyl 4-hydroxybenzoate and 1 gram of propyl 4-hydroxybenzoate were dissolved in 4 l of boiling purified water. In 3 l of this solution were dissolved first 10 grams of 2,3-dihydroxybutanedioic acid and thereafter 20 grams of the A.I. The latter solution was combined with the remaining part of the former solution and 12 l 20 1,2,3-propanetriol and 3 l of sorbitol 70% solution were added thereto. 40 Grams of sodium saccharin were dissolved in 0.5 l of water and 2 ml of raspberry and 2 ml of gooseberry essence were added. The latter solution was combined with the former, water was added q.s. to a volume of 20 l providing an oral solution comprising 5 mg of the active ingredient per teaspoonful (5 ml). The resulting solution was filled in suitable 25 containers.

Example 3-c : CAPSULES

- 20 Grams of the A.I., 6 grams sodium lauryl sulfate, 56 grams starch, 56 grams lactose, 0.8 grams colloidal silicon dioxide, and 1.2 grams magnesium stearate were vigorously stirred together. The resulting mixture was subsequently filled into 1000 suitable 30 hardened gelatin capsules, comprising each 20 mg of the active ingredient.

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Example 4-e : FILM-COATED TABLETSPreparation of tablet core

A mixture of 100 grams of the A.I., 570 grams lactose and 200 grams starch was mixed well and thereafter humidified with a solution of 5 grams sodium dodecyl sulfate and 10 grams polyvinylpyrrolidone in about 200 ml of water. The wet powder mixture was sieved, dried and sieved again. Then there was added 100 grams microcrystalline cellulose and 15 grams hydrogenated vegetable oil. The whole was mixed well and compressed into tablets, giving 10.000 tablets, each containing 10 mg of the active ingredient.

Coating

To a solution of 10 grams methyl cellulose in 75 ml of denaturated ethanol there was added a solution of 5 grams of ethyl cellulose in 150 ml of dichloromethane. Then there were added 75 ml of dichloromethane and 2.5 ml 1,2,3-propanetriol. 10 Grams of polyethylene glycol was molten and dissolved in 75 ml of dichloromethane. The latter solution was added to the former and then there were added 2.5 grams of magnesium octadecanoate, 5 grams of polyvinylpyrrolidone and 30 ml of concentrated colour suspension and the whole was homogenated. The tablet cores were coated with the thus obtained mixture in a coating apparatus.

Example 5-e : INJECTABLE SOLUTION

1.8 Grams methyl 4-hydroxybenzoate and 0.2 grams propyl 4-hydroxybenzoate were dissolved in about 0.5 l of boiling water for injection. After cooling to about 50°C there were added while stirring 4 grams lactic acid, 0.05 grams propylene glycol and 4 grams of the A.I.. The solution was cooled to room temperature and supplemented with water for injection q.s. ad 1 l, giving a solution comprising 4 mg/ml of A.I.. The solution was sterilized by filtration (U.S.P. XVII p. 811) and filled in sterile containers.

Example 6-e : SUPPOSITORIES

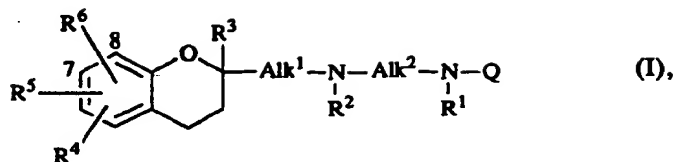
3 Grams A.I. was dissolved in a solution of 3 grams 2,3-dihydroxybutanedioic acid in 25 ml polyethylene glycol 400. 12 Grams surfactant (SPAN®) and triglycerides (Witepsol 555 ®) q.s. ad 300 grams were molten together. The latter mixture was mixed well with the former solution. The thus obtained mixture was poured into moulds at a temperature of 37-38°C to form 100 suppositories each containing 30 mg/ml of the A.I.

Example 7-e : INJECTABLE SOLUTION

60 Grams of A.I. and 12 grams of benzylalcohol were mixed well and sesame oil was added q.s. ad 1 l, giving a solution comprising 60 mg/ml of A.I. The solution was sterilized and filled in sterile containers.

Claims

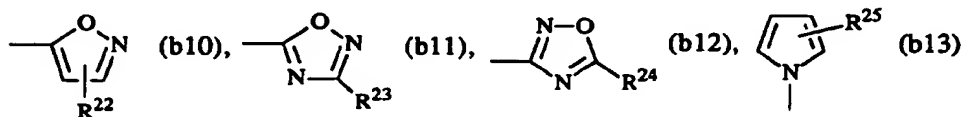
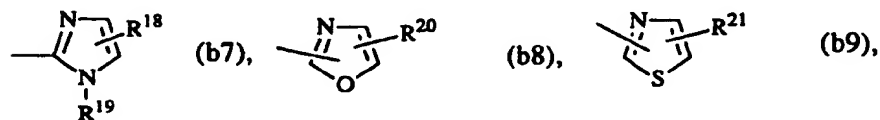
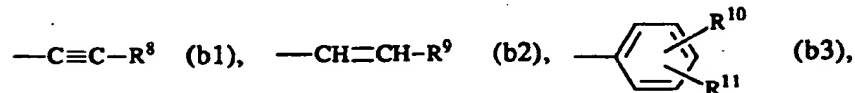
- 5 1. A compound having the formula



- a pharmaceutically acceptable acid or base addition salt thereof, or a stereochemically isomeric form thereof, wherein
- R^1 , R^2 and R^3 each independently are hydrogen or C_{1-6} alkyl;
- R^4 is hydrogen, halo, C_{1-6} alkyl, hydroxy, C_{1-6} alkyloxy, aryloxy or arylmethoxy;
- R^5 and R^6 designate R^{5a} and R^{6a} ,
 wherein R^{5a} and R^{6a} are taken together to form a bivalent radical, which is linked to the 7 and 8 position of the dihydrobenzopyran moiety, and has the formula
- | | | | |
|---|-------|---|--------|
| $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$ | (a1), | $-(\text{CH}_2)_t-\text{Z}-$ | (a9), |
| $-(\text{CH}_2)_n-$ | (a2), | $-\text{Z}-(\text{CH}_2)_t-$ | (a10), |
| $-(\text{CH}_2)_m-\text{X}-$ | (a3), | $-\text{CH}=\text{CH}-\text{Z}-$ | (a11), |
| $-\text{X}-(\text{CH}_2)_m-$ | (a4), | $-\text{Z}-\text{CH}=\text{CH}-$ | (a12), |
| $-\text{CH}=\text{CH}-\text{X}-$ | (a5), | $-\text{NH}-\text{C}(\text{A})=\text{N}-$ | (a13), |
| $-\text{X}-\text{CH}=\text{CH}-$ | (a6), | $-\text{O}-\text{C}(\text{A})=\text{N}-$ | (a14), |
| $-\text{O}-(\text{CH}_2)_t-\text{Y}-$ | (a7), | $-\text{N}=\text{C}(\text{A})-\text{O}-$ | (a15); |
| $-\text{Y}-(\text{CH}_2)_t-\text{O}-$ | (a8), | | |
- in these bivalent radicals one or two hydrogen atoms may be substituted with C_{1-6} alkyl, C_{1-6} alkylcarbonyl or C_{1-6} alkyl-S(O)-;
- n is 3 or 4;
- each X independently is -O-, -S-, -S(O)-, -S(O)₂-, -C(O)-, -NR⁷-;
- each m independently is 2 or 3;
- each Y independently is -O-, -S-, -S(O)-, -S(O)₂-, -C(O)-, -NR⁷-;
- Z is -O-C(O)-, -C(O)-O-, -NH-C(O)-, -C(O)-NH-;
- each t independently is 1 or 2;
- R^7 is hydrogen, C_{1-6} alkyl, C_{1-6} alkylcarbonyl or C_{1-6} alkyl-S(O)-;
- each A independently is hydroxy, C_{1-6} alkyl, C_{1-6} alkyloxy;
- or R^5 and R^6 designate R^{5b} and R^{6b} , wherein R^{5b} is hydrogen and

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R^{6b} is hydroxyC₁₋₆alkyl, carboxylC₁₋₆alkyl, C₁₋₆alkyloxycarbonylC₁₋₆alkyl, trihalomethyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonylC₁₋₆alkyl-S-, carboxylC₁₋₆alkyl-S-, C₁₋₆alkyl-S-, C₁₋₆alkyl-S(O)-, aryl-S-, aryl-S(O)- or R^{6b} is a radical of formula



R⁸ and R⁹ each independently are hydrogen, carboxyl, C₁₋₆alkyloxycarbonyl, aminocarbonyl, mono- or di(C₁₋₆alkyl)aminocarbonyl;

15 R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶ and R¹⁷ each independently are hydrogen, halo or C₁₋₆alkyl;

R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴ and R²⁵ each independently are hydrogen or C₁₋₆alkyl;

20 or R⁵ and R⁶ designate R^{5c} and R^{6c} in which case R⁴ can only mean hydrogen;

and R^{5c} and R^{6c} each independently are hydrogen, halo, C₁₋₆alkyl, C₃₋₆alkenyl, C₃₋₆alkynyl, hydroxy, C₁₋₆alkyloxy, cyano, aminoC₁₋₆alkyl, carboxyl,

25 C₁₋₆alkyloxycarbonyl, nitro, amino, aminocarbonyl, C₁₋₆alkylcarbonylamino, or mono- or di(C₁₋₆alkyl)amino;

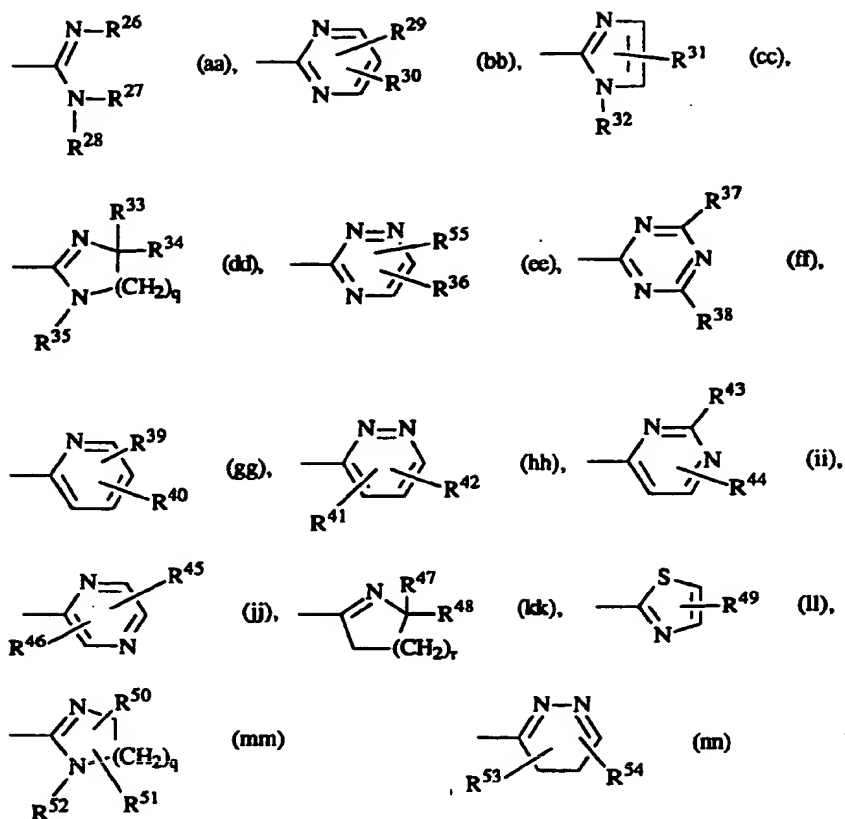
Alk¹ is C₁₋₅alkanediyl;

Alk² is C₂₋₁₅alkanediyl;

Q is a radical of formula

30

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5 wherein

R²⁶ is hydrogen, cyano, aminocarbonyl or C₁₋₆alkyl;

R²⁷ is hydrogen, C₁₋₆alkyl, C₃₋₆alkenyl, C₃₋₆alkynyl, C₃₋₆cycloalkyl or arylC₁₋₆alkyl;

R²⁸ is hydrogen or C₁₋₆alkyl; or

R²⁷ and R²⁸ taken together form a bivalent radical of formula -(CH₂)₄-, -(CH₂)₅-, or a

15 piperazine which is optionally substituted with C₁₋₆alkyl;

R²⁹, R³⁰, R³¹, R³⁶, R³⁷, R³⁸, R³⁹, R⁴⁰, R⁴¹, R⁴², R⁴³, R⁴⁴, R⁴⁵, R⁴⁶, R⁵³, R⁵⁴ and R⁵⁵ each independently are hydrogen, hydroxy, halo, C₁₋₆alkyl, C₁₋₆alkyloxy, aryloxy, arylC₁₋₆alkyl, C₁₋₆alkylthio, cyano, amino, mono- or di(C₁₋₆alkyl)amino, mono- or di(C₃₋₆cycloalkyl)amino, aminocarbonyl, C₁₋₆alkyloxycarbonylamino,

20 C₁₋₆alkylaminocarbonylamino, piperidinyl, pyrrolidinyl;

R³², R³⁵ and R⁵² each independently are hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, or arylC₁₋₆alkyl;

q is 1, 2 or 3;

R³³ and R³⁴ are each hydrogen or taken together with the carbon atom to which they are connected they can form C(O);

25

r is 1, 2 or 3;

R⁴⁷ and R⁴⁸ are each hydrogen or taken together with the carbon atom to which they are connected they can form C(O);

R⁴⁹ is hydrogen, halo or C₁₋₆alkyl;

- 5 R⁵⁰ is hydrogen and R⁵¹ is hydroxy; or R⁵⁰ and R⁵¹ taken together may form a bivalent radical of formula (CH₂)₃ or (CH₂)₄ which is optionally substituted with C₁₋₆alkyl; aryl is phenyl optionally substituted with hydroxy, halo, C₁₋₆alkyl, C₁₋₆alkyloxy;

- 10 with the proviso that when R⁴ is hydrogen and R⁵ and R⁶ designate R^{5c} and R^{6c} then Q must be a radical of formula (gg); (hh); (ii); (jj); (kk); (ll); (mm); (nn); a radical of formula (aa) wherein R²⁷ is C₃₋₆cycloalkyl or arylC₁₋₆alkyl; a radical of formula (aa) wherein R²⁷ and R²⁸ taken together with the nitrogen atom to which they are attached form a piperazine which is optionally substituted with C₁₋₆alkyl; a radical of formula (bb) wherein R²⁹ is hydroxy on a carbon atom adjacent to a nitrogen atom; a radical of
15 formula (dd) wherein R³⁵ is hydrogen and R³³ and R³⁴ taken together with the carbon atom to which they are attached form C(O); a radical of formula (ee) wherein R⁵⁵ is arylC₁₋₆alkyl.

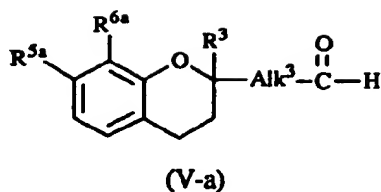
- 20 2. A compound as claimed in claim 1 wherein R¹, R², R³ and R⁴ are as defined in claim 1 and wherein R⁵ and R⁶ designate R^{5a} and R^{6a}, wherein in formulas (a7) and (a8) t is 2; Q is a radical of formula (aa), (bb), (cc), (dd) wherein q is 1 or 2, (ee) wherein R⁵⁵ is hydrogen, (ff), (gg), (hh), (ii), (jj), (kk) wherein q is 1 or 2, (ll).

- 25 3. A compound as claimed in claim 1, wherein wherein R¹, R², R³ are as defined in claim 1, R⁴ is hydrogen, halo, C₁₋₆alkyl; R⁵ and R⁶ designate R^{5b} and R^{6b}, R^{5b} being hydrogen and R^{6b} is hydroxyC₁₋₆alkyl, carboxylC₁₋₆alkyl, C₁₋₆alkyloxycarbonylC₁₋₆alkyl, trihalomethyl, a radical of formula (b1), (b2), (b3), (b4), (b5), (b6), (b7), (b8), (b9), (b10), (b11), (b12); Q is a radical of formula (aa), (bb), (cc), (dd) wherein q is 1 or 2, (ee) wherein R⁵⁵ is hydrogen, (ff), (gg), (hh), (ii), (jj), (kk) wherein q is
30 1 or 2, or (ll).

4. A compound as claimed in claim 1 wherein R¹, R², R³ are as defined in claim 1, R⁴ is hydrogen and R⁵ and R⁶ designate R^{5c} and R^{6c}, and Q is a radical of formula (gg); (hh); (ii); (jj); (kk) wherein q is 1 or 2; (ll); a radical of formula (bb) wherein R²⁹ is
35 hydroxy on a carbon atom adjacent to a nitrogen atom; or a radical of formula (dd) wherein R³⁵ is hydrogen and R³³ and R³⁴ taken together with the carbon atom to which they are attached form C(O) and q is 1 or 2.

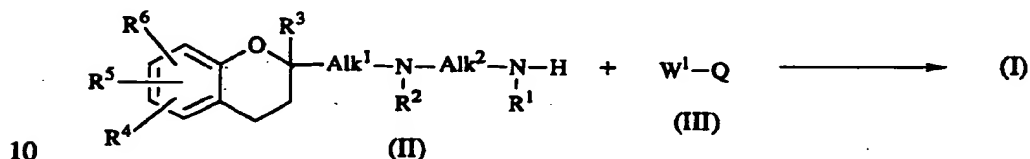
5. A compound as claimed in claim 1, wherein the compound is
 $N-[(2,3,4,7,8,9\text{-hexahydrobenzo}[2,1\text{-}b:3,4\text{-}b']\text{dipyrans-2-yl)methyl}]-N'$
 $2\text{-pyrimidinyl-1,3-propanediamine}$; $N-[(2,3,4,7,8,9\text{-hexahydrocyclopenta}[h]\text{-}$
 5 $1\text{-benzopyran-2-yl)methyl}]-N'$ $2\text{-pyrimidinyl-1,3-propanediamine}$; $(\pm)\text{-}N-[(2,3,4,8,9,$
 $10\text{-hexahydrobenzo}[2,1\text{-}b:3,4\text{-}b']\text{dipyrans-2-yl)methyl}]-N'$ $2\text{-pyrimidinyl-1,3-propane}$
 diamine ; $N-[(3,4,7,8,9,10\text{-hexahydro-2H-naphtho}[1,2\text{-}b]\text{pyran-2-yl)methyl}]-$
 N' $2\text{-pyrimidinyl-1,3-propanediamine}$; $N\text{-(4,5-dihydro-1H-imidazol-2-yl)-}N'$
 $[(2,3,4,7,8,9\text{-hexahydrocyclopenta}[h]\text{-}1\text{-benzopyran-2-yl)methyl}]\text{-1,3-propanediamine}$;
 10 $N-[(2,3,4,7,8,9\text{-hexahydrobenzo}[2,1\text{-}b:3,4\text{-}b']\text{dipyrans-2-yl)methyl}]-N'$ $-(1,4,5,6\text{-}$
 $\text{tetrahydro-2-pyrimidinyl})\text{-1,3-propanediamine}$; $N-[(2,3,4,7,8,9\text{-hexahydro}$
 $\text{cyclopenta}[h]\text{-}1\text{-benzopyran-2-yl)methyl}]-N'$ $-(1,4,5,6\text{-tetrahydro-2-pyrimidinyl})\text{-}$
 $1,3\text{-propanediamine}$; $N-[(2,3,7,8\text{-tetrahydro-9H-pyrano}[2,3\text{-}f]\text{-}1,4\text{-benzodioxin-9-}$
 $\text{yl)methyl}]-N'$ $-(1,4,5,6\text{-tetrahydro-2-pyrimidinyl})\text{-1,3-propanediamine}$;
 15 $N-[(3,4,7,8,9,10\text{-hexahydro-2H-naphtho}[1,2\text{-}b]\text{pyran-2-yl)methyl}]-N'$ $-(1,4,5,6\text{-}$
 $\text{tetrahydro-2-pyrimidinyl})\text{-1,3-propanediamine}$;
 $\text{methyl } 3\text{-[6-fluoro-3,4-dihydro-2-[[[3-(2-pyrimidinylamino)propyl]amino]methyl]-2H-}$
 $1\text{-benzopyran-8-yl]-2-propenoate}$; $N-[[6\text{-fluoro-8-(2-furanyl)-3,4-dihydro-}$
 $2H\text{-}1\text{-benzopyran-2-yl)methyl}]-N'$ $2\text{-pyrimidinyl-1,3-propanediamine}$;
 20 $N-[[6\text{-fluoro-3,4-dihydro-8-(2-thienyl)-2H-}1\text{-benzopyran-2-yl)methyl}]-N'$ $-(1,4,5,6\text{-}$
 $\text{tetrahydro-2-pyrimidinyl})\text{-1,3-propanediamine}$;
 $N-[(3,4\text{-dihydro-2H-}1\text{-benzopyran-2-yl)methyl}]-N'$ $-(3,4,5,6\text{-tetrahydro-}$
 $2\text{-pyridinyl})\text{-1,3-propanediamine}$; $N^4\text{-[3-[(3,4-dihydro-2H-}1\text{-benzopyran-}$
 $2\text{-yl)methyl]amino]propyl}]-N^2\text{-methyl-2,4-pyrimidinediamine}$; a pharmaceutically
 25 acceptable acid addition salt, or stereochemically isomeric form thereof.
6. A composition comprising a pharmaceutically acceptable carrier and as an active
 ingredient a therapeutically amount of a compound as claimed in claim 1.
- 30 7. A process of preparing a composition as claimed in claim 5, characterized in that a
 therapeutically effective amount of a compound as claimed in claim 1 is intimately
 mixed with a pharmaceutically acceptable carrier.
8. An intermediate of formula (V-a), a pharmaceutically acceptable addition salt thereof
 35 or a stereochemically isomeric form thereof, wherein R^3 , R^{5a} and R^{6a} are as defined
 in claim 1 and wherein alk^3 is $\text{C}_{1-4}\text{alkanediyl}$.

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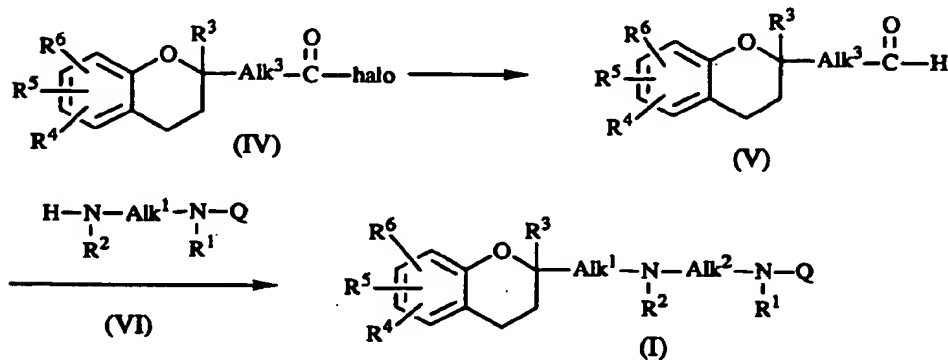


9. A compound as claimed in claim 1 for use as a medicine.

10. A process of preparing a compound as claimed in claim 1, characterized by
 a) reacting an intermediate of formula (II), wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , Alk^1 and Alk^2 are as defined in claim 1, with a reagent of formula (III), wherein Q is as defined in claim 1 and W^1 is a reactive leaving group;

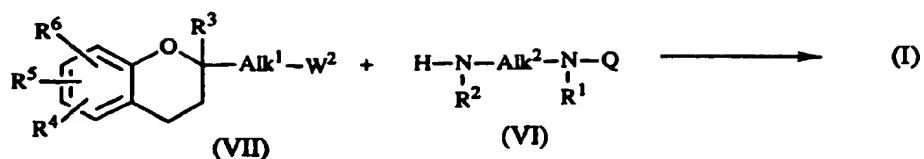


- b) reducing an acyl derivative of formula (IV), wherein R^3 , R^4 , R^5 and R^6 is as defined in claim 1, Alk^3 is C_{1-4} alkanediyl, and reductively N -alkylating an intermediate of formula (VI), wherein R^1 , R^2 , Alk^2 and Q are as defined in claim 1 with the resulting aldehyde of formula (V)
- 15

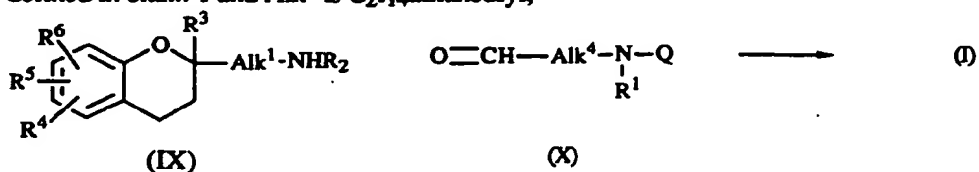


- c) N -alkylating an amine of formula (VI) with an intermediate of formula (VII), wherein R^3 , R^4 , R^5 , R^6 and Alk^1 are as defined in claim 1 and W^2 is a reactive leaving group;
- 20

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- d) reductive N-alkylating an amine of formula (IX), wherein R², R³, R⁴, R⁵, R⁶ and Alk¹ are defined in claim 1, with an aldehyde of formula (X), wherein R¹ and Q are as defined in claim 1 and Alk⁴ is C₂-₁₄alkanediyl;



- and optionally converting the compounds of formula (I) into each other by a functional group transformation reaction; and, if desired, converting a compound of formula (I) into a therapeutically active non-toxic acid addition salt, or conversely, converting an acid addition salt into a free base form with alkali; and/or preparing stereochemically isomeric forms thereof.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 94/02703

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D493/04 C07D405/12 C07D311/58 A61K31/35

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 352 613 (BAYER) 31 January 1990 see page 57; claims; example 59 ----	1,6-10
P,X	WO,A,93 17017 (JANSSEN) 2 September 1993 see the whole document -----	1,6-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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- "O" document referring to an oral disclosure, use, exhibition or other means
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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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Date of the actual completion of the international search

24 November 1994

Date of mailing of the international search report

- 6. 12. 94

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 94/02703

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		CN-B-	1024667	25-05-94
		DE-D-	58907493	26-05-94
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WO-A-9317017	02-09-93	AU-B-	3499193	13-09-93
		CA-A-	2117483	02-09-93
		CN-A-	1079470	15-12-93
		FI-A-	943928	26-08-94
